Decision Summary

The Centers for Medicare and Medicaid Services (CMS) proposes that platelet-rich plasma (PRP) – an autologous blood-derived product, will be covered only for the treatment of chronic non-healing diabetic, venous and/or pressure wounds and only when the following conditions are met:

The patient is enrolled in a randomized clinical trial that addresses the following questions using validated and reliable methods of evaluation. Clinical study applications for coverage pursuant to this National Coverage Determination (NCD) must be received by [2 YEARS FROM THE DATE OF FINAL DM ISSUANCE], 2014.

The clinical research study must meet the requirements specified below to assess the effect of PRP for the treatment of chronic non-healing diabetic, venous and/or pressure wounds. The clinical study must address:

Prospectively, do Medicare beneficiaries that have chronic non-healing diabetic, venous and/or pressure wounds who receive well-defined optimal usual care along with PRP therapy, experience clinically significant health outcomes compared to patients who receive well-defined optimal usual care for chronic non-healing diabetic, venous and/or pressure wounds as indicated by addressing at least one of the following:

a. Complete wound healing?
b. Ability to return to previous function and resumption of normal activities?
c. Reduction of wound size or healing trajectory which results in the patient's ability to return to previous function and resumption of normal activities?

The required randomized clinical trial (RCT) of PRP must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the RCT is to test whether PRP improves the participants' health outcomes.
b. The RCT is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The RCT does not unjustifiably duplicate existing studies.
d. The RCT design is appropriate to answer the research question being asked in the study.
e. The RCT is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The RCT is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46.
g. All aspects of the RCT are conducted according to appropriate standards of scientific integrity set by the International Committee of Medical Journal Editors

(http://www.icmje.org).
h. The RCT has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for coverage with evidence development (CED).
i. The RCT is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
j. The RCT is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The RCT study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors

(http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
l. The RCT protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
m. The RCT protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with §1142 of the Social Security Act (the Act), the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

We are requesting public comments to this proposed decision pursuant to §1862(l) of the Act. After consideration of the public comments, we will issue a final determination responding to the public comments consistent with §1862(l)(3) of the Act.

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Proposed Decision Memo

TO: Administrative File: CAG-00190R3
Autologous Blood-Derived Products for Chronic Non-Healing Wounds (Third Reconsideration)

FROM:

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SUBJECT: Proposed Decision Memorandum for CAG-00190R3
Autologous Blood-Derived Products for Chronic Non-Healing Wounds
DATE: May 9, 2012

I. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes that platelet-rich plasma (PRP) – an autologous blood-derived product, will be covered only for the treatment of chronic non-healing diabetic, venous and/or pressure wounds and only when the following conditions are met:

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II. Background

A. Wound Etiology and the Wound Healing Process

Wound healing is a dynamic, interactive process that involves multiple cells and proteins. There are three progressive stages of normal wound healing, and the typical wound healing duration is about four weeks. While cutaneous wounds are a disruption of the normal anatomic structure and function of the skin, subcutaneous wounds involve tissue below the skin's surface. Wounds are categorized as either acute or chronic. In acute wounds, the normal wound healing stages are not yet completed but it is presumed they will be resulting in orderly and timely wound repair. However, in a chronic wound, the wound has failed to progress through the normal wound healing stages and repair itself within a sufficient time period.

A wound is a disruption of normal anatomic structure and function and can range from a simple scratch to an interruption that goes through tissue and muscle down to bone. Acute wounds are wounds of relatively new onset that heal in an orderly fashion, first by reestablishing epithelial integrity, then by laying down new collagen to strengthen the damaged tissue. The result is re-establishment of anatomic and functional integrity. Fortunately, most wounds are acute wounds that heal rapidly and uneventfully.

The process of wound healing involves an integrated series of cellular, physiologic, biochemical, and molecular events. The stages of wound healing are defined as inflammatory, proliferative, and remodeling. The inflammatory phase is characterized by platelet accumulation, coagulation, and leukocyte migration into the wound site. During this phase, the platelets adhere to collagen to form a vascular plug and the leukocytes, along with macrophages, begin removing cellular debris and bacteria. This inflammatory phase occurs during the first three to four days after a wound presents. The cellular interactions in this phase help to provide a temporary stable wound environment.

The proliferative phase, also termed fibroblastic, is characterized by the regeneration of epidermis, angiogenesis, and the proliferation of fibroblast that forms collagen. Angiogenesis, the formation of a new vascular supply, is important for allowing the nutrition required in the healing process to invade the wound area. Collagen formation plays a prominent role in wound healing and there are over 20 different types of collagen in the human body. Type III collagen, which is part of the granulation tissue, is produced by fibroblasts during the proliferative phase. The re-epithelialization helps to restore the cutaneous barrier. All of these physiologic events normally occur during the 10 to 14 day period after a wound presents.

The third and final phase of wound healing, the remodeling phase, takes place from a period of months up to two years (Bhanot & Alexi 2002). This phase is characterized by collagen synthesis and degradation. The type III collagen is replaced by type I collagen that is instrumental in decreasing the wound size through contraction. Contractile forces are produced by contractile proteins as well as the presence of type I collagen that ultimately results in scar formation. At the end of remodeling, the resulting scar tissue is approximately only 80% the strength of normal skin (Bhanot & Alexi 2002).

The stages of wound healing are sequential in the normal healing process of acute wounds. Many chronic wounds fail to complete all the stages of normal wound healing (Loots et al. 1998). When the healing process fails to progress properly and the wound persists for longer than one month, it may be described as a chronic wound. In chronic wounds, the healing process is disrupted by some underlying abnormality that prolongs the inflammatory phase, resulting in poor anatomic and functional outcome. Common underlying abnormalities include diabetes, abnormal external pressures and arterial or venous circulatory insufficiency.

Since the etiology of wounds varies, the most effective therapy may vary as well. For example, the etiology of a pressure ulcer relates to unrelieved pressure on the skin, whereas the origin of a diabetic ulcer has other etiologies. Therefore, it is difficult to generalize the findings from studies on therapy from one type of ulcer to another type. According to the "Guidance for Industry-Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment," the Food and Drug Administration (FDA) states that "Wounds differ pathophysiologically, making it difficult-if not impossible -to generalize results obtained from a trial conducted in patients with one type of wound to those with another wound type. Separate safety and efficacy data should be submitted for each wound type for which an indication is sought" (FDA 2000).

Wound care must be directed at providing an environment in which the body can effectively carry out the healing process. Conventional or standard therapy for chronic wounds involves local wound care as well as systemic measures. Standard care considerations to promote wound healing include debridement or removal of necrotic tissue, wound cleansing and dressings that promote a moist wound environment. Systemic treatments include the use of antibiotics to control infection and optimizing nutritional status. Early concepts in wound management involved soaking the wound in antiseptics to kill bacteria and then covering the wound with a dry dressing. As the biology of wound healing has become better understood, a variety of wound care strategies and products have been developed to help aid the healing process. Various new dressings such as alginates, hydrogels, films, and foam products are now used. Additionally, newer techniques such as negative pressure dressings, radiant heat, electrical stimulation and hyperbaric oxygen are also being investigated.

There are other conventional therapeutic modalities that may apply to certain subgroups of patients depending on their type of wound. Specific conventional therapies for venous ulcers include the use of compression devices aimed at decreasing venous stasis. Patients that have pressure ulcers require frequent repositioning to redistribute the pressure that is causing the ulcers. Good glucose control for diabetic foot ulcers and establishing adequate circulation for arterial ulcers are other ulcer-specific therapies.

The multitude of wound care regimens demonstrates the complexity of wound care management and the lack of one, universally proven treatment strategy. Knowledge of the pathophysiology of healing combined with realistic patient outcomes will help guide the clinician in choosing the wound care treatment plan. Lait and Smith reported that no single wound dressing is sufficient for all types of wounds and few are ideally suited for the treatment of a single wound through all phases of healing (Lait & Smith 1998).

Some wound care specialists have proposed that chronic wounds do not heal due to a lack of vital growth factors that are believed to be deficient in chronic wounds (Belden 1999). Several sources noted by Payne have proposed that this deficiency is due to repeated trauma, ischemia, and infection that increases the level of pro-inflammatory cytokines, increases the level of matrix metalloproteinases, decreases the presence of tissue inhibitors of metalloproteins, and lowers the level of growth factors (Payne et al. 2001).

B. Role of Platelets and the Development of Platelet-rich Plasma

Originally, it was thought that platelets were important only for clot formation. However, it is now clear that platelets contain a large number of growth factors. The exact number and purpose of all of the growth factors is not known. Four growth factors are most frequently cited (Atri et al. 1990). The first is the platelet-derived angiogenesis factor that causes new capillary formation from the existing microvasculature (Knighton et al. 1982). Platelet-derived epidermal growth factor and platelet factor 4 (considered to be a chemoattractant for neutrophils) have also been identified. The fourth type is platelet-derived growth factor (PDGF), which is a potent fibroblast mitogen and chemoattractant.

With this knowledge, Dr. David L. Knighton developed, in 1985, a system to obtain multiple growth factors from platelets and started treating patients at the University of Minnesota. A retrospective study based on the first patients treated with PDGF was published in 1986 (Knighton et al. 1986). The first prospective trial was then conducted by Knighton et al. and the results were published in 1990 (Knighton et al. 1990). Dr. Knighton obtained a patent in 1992 on products released from platelets (i.e., platelet releasate) that are used for tissue repair. Procuren Solution® produced by CuraTech (which later became Curative Health Services) was available throughout the United States through 150 wound care centers starting in 1986. Marketing of Procuren Solution® ceased in 2001. However, various PDGF products, which contain multiple proteins like Procuren but do not contain cells like PRP, are in use for patient care.

In 1997, FDA approved the biologics license application of Ortho-McNeil Johnson Pharmaceuticals, Inc. to market Regranex® (becaplermin) Gel 0.01%. The recombinant human platelet-derived growth factor-BB (rhPDGF-BB) was approved for the treatment of lower extremity diabetic neuropathic ulcers that extend into subcutaneous tissue or beyond and have an adequate blood supply. It was not approved for superficial ulcers that do not extend through the dermis into subcutaneous tissue or ischemic diabetic ulcers. This proposed decision memorandum is primarily focused on autologous products, and since becaplermin is not an autologous product, it is not addressed in this proposed memorandum.

PRP is produced in an autologous or homologous manner. Autologous PRP is comprised of blood from the patient who will ultimately receive the PRP. Alternatively, homologous PRP is derived from blood from multiple donors. Blood is donated by the patient and centrifuged to produce an autologous gel that has been used in the treatment of acute wounds as well as chronic, non-healing cutaneous wounds that persist for 30 days or longer and fail to properly complete the healing process. Autologous blood derived products for chronic, non-healing wounds include:

1. PDGF products (such as Procuren®), and
2. PRP products (such as AutoloGel™).

In an attempt to improve the healing process, wound specialists have become more interested in autologous PRP produced by an apheresis process first developed by Charles Worden in 1998. In this process, autologous blood (blood donated by the patient) is centrifuged to produce a concentrate high in both platelets and plasma proteins. Individual growth factors are not identified or separated during this process. Additives are used to change the consistency of the product. Autologous PRP has been used for a variety of purposes such as an adhesive in plastic surgery and filler for acute wounds. It is also now being used on chronic wounds. PRP is different from earlier products in that it contains whole cells including white cells, red cells, plasma, platelets, fibrinogen, stem cells, macrophages, and fibroblasts and is used by physicians in a clinical or surgical setting. PDGF does not contain cells and was previously marketed as a product to be used by patients at home. Both PDGF and PRP gels are derived from the patient's own blood.

PRP is frequently administered as a spray, or a gel. Other systems and protocols have been used to administer PRP. In this proposed decision memorandum as in previous ones, CMS is evaluating PRP as a service, and not a specific system for administrating PRP.

III. History of Medicare Coverage

In 1992, CMS issued a national non-coverage determination for platelet-derived wound healing formulas intended to treat patients with chronic, non-healing wounds.

On December 15, 2003, CMS issued a national non-coverage determination for use of autologous PRP for the treatment of chronic non-healing cutaneous wounds except for routine costs when used in accordance with the clinical trial policy defined in section 310.1 of the National Coverage Determinations Manual.

On April 27, 2006, CMS issued an NCD to correct the erroneous potential for local coverage of becaplermin, printed in section 270.3 of the National Coverage Determination manual, entitled "Blood-Derived Products for Chronic Non-Healing Wounds." CMS deleted the erroneous sentences and inserted the correct statement that "Coverage for treatments utilizing becaplermin, a non-autologous growth factor for chronic non-healing subcutaneous wounds, will remain nationally non-covered under Part B based on §1861(s)(2)(A) and (B) because this product is usually administered by the patient."

On March 19, 2008, CMS issued a non-coverage determination for the use of autologous blood-derived products for the treatment of acute wounds where PRP is applied directly to the closed incision site, and for dehiscent wounds. Current non-coverage for chronic, non-healing cutaneous wounds was maintained.

A. Current Request

On October 4, 2011, Cytomedix submitted a formal request to reopen and revise section 270.3 of the Medicare National Coverage Determinations Manual, which addresses Autologous Blood-Derived Products for Chronic Non-Healing Wounds. They stated that PRP is the prevalent blood-derived therapeutic product used for treating chronic non-healing wounds.

Cytomedix submitted new studies and requested CMS re-evaluate the coverage of autologous PRP gel for the treatment of the following chronic wounds: diabetic, venous, and/or pressure ulcers.

Alternatively, Cytomedix requested that CMS cover PRP gel through an NCD with data collection as a condition of coverage; and requested that this would provide a practical means by which CMS could obtain the necessary data to evaluate the performance of PRP gel and to confirm the outcomes presented in their request.

B. Benefit Category

For an item or service to be covered by the Medicare program, among other things, it must meet one of the statutorily defined benefit categories outlined in the Act.

There is no specific Medicare benefit category for autologous blood-derived products for treatment of chronic non-healing wounds. However, these services, at a minimum, fall within the benefit categories of physician's service (§1861(s)(1) of the Act) and "incident to" a physician's service (§1861(s)(2)(A) of the Act).

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

November 9, 2011	CMS formally opened a third reconsideration of the national coverage analysis on Autologous Blood-Derived Products for Chronic Non-Healing Wounds. The initial public comment period opened.

December 9, 2011	The initial public comment period closed.
February 7, 2012	CMS had a conference call with Cytomedix, the requestor, and its physician representatives, who discussed an overview of a trial that was pending submission for publication. The results of this trial were not available during this call. Unpublished, and therefore, non-peer-reviewed, information generally is accorded less weight than published and peer-reviewed material.

V. FDA Status

It is important to note that FDA clearance is for the equipment in the AutoloGel™ System, and not the actual PRP gel produced from this kit. The FDA has not considered the safety and/or efficacy of the gel.

The AutoloGel™ System has been cleared by the FDA under Section 510(k). According to FDA documents a "510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent (SE), to a legally marketed device (21 CFR 807.92(a)(3)) that is not subject to premarket approval (PMA). Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims. A legally marketed device, as described in 21 CFR 807.92(a)(3), is a device that was legally marketed prior to May 28, 1976 (preamendments device), for which a PMA is not required, or a device which has been reclassified from Class III to Class II or I, or a device which has been found SE through the 510(k) process. The legally marketed device(s) to which equivalence is drawn is commonly known as the "predicate." Although devices recently cleared under 510(k) are often selected as the predicate to which equivalence is claimed, any legally marketed device may be used as a predicate." (FDA 2010)

On September 19, 2007, the FDA described the AutoloGel™ System as "a device consisting of a tabletop centrifuge… and a wound dressing convenience kit…comprised of legally-marketed products…" The FDA stated the device "is intended to be used at point-of-care for the safe and rapid preparation of PRP gel from a small sample of a patient's own blood. Under the supervision of a healthcare professional, the PRP gel produced by the AutoloGel™ System is suitable for exuding wounds, such as leg ulcers, pressure ulcers and for the management of mechanically or surgically-debrided wounds." The FDA further concluded, "Based on the clinical performance information, it can be concluded that AutoloGel is substantially equivalent to the marketed wound dressing IPM Wound Gel." (FDA 510(k) letter BK06007)

VI. General Methodological Principles

In general, when making NCDs under §1862(a)(1)(A), CMS evaluates relevant clinical evidence to determine whether or not the evidence supports a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or improves the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for Medicare beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary under §1862(a)(1)(A) of the Act.

A detailed account of the methodological principles of study design that the Agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public comments sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform the public of its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

This section provides a summary of the evidence that CMS considered during the review. There were a number of systematic reviews and meta-analyses found in the medical literature that investigated the use of PRP in patients with acute as well as chronic wounds. Though results of both types of wounds were reported, the primary focus of this NCD is the effects of PRP on chronic wounds. A number of prospective studies such as comparative studies, and cohort studies, as well as retrospective studies were also found. They also were reviewed for this analysis.

B. Discussion of Evidence Reviewed

1. Question and Outcomes

Is the evidence sufficient to determine that Medicare beneficiaries who have chronic non-healing diabetic, venous and/or pressure wounds that receive PRP therapy experience clinically significant health outcomes as indicated by at least one of the following:

a. Complete wound healing?
b. Ability to return to previous function and resumption of normal activities?

The ultimate goal for patients with chronic wounds is complete healing and improved quality of life. These are the primary outcome measures. A number of secondary outcome measures exist, and they may also be important to patient well-being. Wounds may, depending on their anatomic location and severity, limit range of joint motion and ambulation. Ideally, a wound would be completely cured and would not recur. Avoidance of infection and elimination of pain are essential in the recovery process. Chronic wounds that are malodorous may be embarrassing for a patient and thus can lead to social isolation. Improvement in these outcomes should culminate in increased activity which will lead to resumption of normal activities and improved quality of life.

2. External Technology Assessment

CMS did not request an external technology assessment (TA) on this topic.

On January 19, 2012, the Cochrane database, the NICE database, the Blue Cross/Blue Shield TEC database, and the Canadian Agency for Drugs and Technologies in Health database were searched using the terms "wound care," "platelet gel," "platelet lysate," "platelet-derived wound healing factor" and "platelet-rich plasma." No technology assessments were found.

AHRQ released a TA dated March 8, 2005 titled "Usual Care in the Management of Chronic Wounds: A Review of the Recent Literature." This technology assessment presented a broad review of the products, techniques, and protocols used in wound management but did not address autologous PRP specifically except to state that growth factors "show promise but need further, more rigorous evaluation." (AHRQ 2005)

AHRQ also released a TA dated May 26, 2009, which evaluated the use of Negative-Pressure Wound Therapy; however, this TA did not address the use of PRP in patients with chronic non-healing diabetic, venous and/or pressure wounds. Currently, AHRQ is performing a TA on Skin Substitutes for Treating Chronic Wounds. We will determine whether the use of PRP is addressed in this TA once it is publicly available.

3. Internal Technology Assessment

Literature search methods

The reviewed evidence was gathered from articles submitted by the NCD requester, submitted during the public comment period, and from a literature search of Pub Med, Cochrane Library, EMBASE as well as other sources, such as the TRIP Database, performed by the CMS staff.

Search terms used to review the medical literature include the following: platelet-rich plasma, platelet-rich plasma gels, PRP, PRP gel(s), autologous plasma rich in platelets, autologous platelet gel, autologous platelet-rich plasma gel, preparation rich in growth factors (PRGF), platelet-rich and platelet poor plasma, platelet gel, autologous platelet lysate, platelet releasate, platelet derived growth factors (PDGF), autologous platelet-derived wound healing factors (PDWHF), wounds, chronic wounds, chronic non-healing wounds, dehiscence wounds, diabetic ulcers, venous ulcers, and pressure ulcers. Only sources provided in English were used. The following terms are considered synonymous to PRP: platelet releasate, platelet lysate, PDWHF, and PDGF.

The NCD requesters provided the full text of 149 articles as part of the reconsideration materials. We also received a number of full text articles as well as references to articles from commenters during the initial comment period, much of which were duplications of full text articles submitted by the requester. Using the above mentioned search terms, over 8,000 citations were identified. Neither the Cochrane Library review nor EMBASE provided any additional studies, but the Cochrane Library currently has posted a protocol for a systematic review of autologous PRP for the treatment of chronic wounds.

A large number of these articles were excluded from this evaluation because they were clinical summary review articles that do not provide primary evidence (e.g., Akingboye et al. 2010; Everts et al. 2006; Peitramaggiori et al. 2006), addressed the use of PRP in acute wounds (e.g., Almdahl et al. 2011; Englert et al. 2006; Fanning et al. 2007; Trowbridge et al. 2005), discussed PRP usage in conjunction with other treatment modalities (e.g., Cervelli et al. 2010; Gurvich et al. 2008; Klayman et al. 2006), discussed PRP used in orthopedic procedures (e.g., Christgau et al. 2006; Jenis et al. 2006; Simon et al. 2004), discussed PRP usage in dental procedures (e.g., Babbush et al. 2003; Griffin et al. 2004; Marx 2004), or discussed the use of PRP in ear, nose and throat (ENT) procedures (e.g., Kassolis et al. 2005; Pomerantz et al. 2005; Steigmann et al. 2005).

The medical literature also had a large number of studies that reported outcomes as a percentage of wound surface healing and as healing trajectory (Anitua et al. 2007; van Rijswijk & Polansky 1994; Benigni et al. 2007; Coerper et al. 2008; Phillips et al. 2000; Robson et al. 2000; Sheehan et al. 2003; Snyder, et al. 2010; van Rijswijk et al. 2011; van Rijswijk & Polansky 1994; de Leon et al. 2011; Frykberg et al. 2010; Sell et al. 2010). Some of these studies were designed to show that reduction in chronic wound size over a specified period of time was a good predictor of complete healing. Though these articles are of interest, they do not address the key outcomes, complete healing and/or the patient's ability to return to previous function and resumption of normal activity, which CMS considers pertinent clinical health outcomes in patients with chronic wounds. Therefore, these studies were also excluded from this analysis.

Other studies were excluded because they were duplicate studies, cost-effectiveness studies, case studies/series, reported outcomes not of interest to CMS, used freeze-dried PRP preparations or allogenic PRP frozen platelets, used homologous PRP, or were animal studies.

The following tables with summaries of the literature analysis can be found in Appendix B:

Table 1: Partial List of Excluded Studies

Table 2: Randomized Clinical Trials

Table 3: Other Prospective Studies

Table 4: Retrospective Studies

Systematic Review/Meta-Analysis

In a review of the medical literature, there were three pertinent systematic reviews/meta-analyses found addressing at least tangentially the use of PRP in the treatment of patients with chronic wounds.

Margolis DK, Kantor J, Berlin J. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. Diabetes Care. 1999;22(5):692-695.

One of the first meta-analysis performed to evaluate treatments of diabetic neuropathic foot ulcers was conducted by Margolis et al. Its aim was to determine the percentage of patients with neuropathic diabetic ulcers that received good wound care within a defined period of time. PRP was not one of the treatments explored or considered in this study.

Carter MJ, Fylling CP, Li WW, de Leon JM, et al. Analysis of run-in and treatment data in a wound outcomes registry: clinical impact of topical platelet -rich plasma gel on healing trajectory. Int Wound J. Dec 2011;8(6)638-50.

Using RCTs and comparative groups, Carter et al. performed a systematic review on the use of autologous platelet-rich plasma (intervention group) compared to standard wound care (control group) in cutaneous wounds. The systematic review looked at articles published between 2001 and 2011. Outcomes of interest included healing information such as complete or partial wound healing, time to heal, healing trajectory, velocity or rate, and wound size reduction. The assessment included publications from peer-reviewed journals (which included articles, brief articles, case studies or letters to the editor), as well as materials presented at scientific meetings (e.g., abstracts, posters). Eligible studies included investigations of patients with cutaneous ulcers or wounds (including dehisced wounds, open surgical wounds, acute or chronic wounds) that were treated with activation-processed PRP. Patients with mixed origin wounds, subsets of different wound types, surgical wounds treated with PRP prior to closure and opening, and surgical wounds treated with PRP were also included in the analysis. Inclusion eligibility required PRP studies to have a control treatment group (e.g. placebo, wound care treatment). Non-inferiority trials that involved two types of PRP treatments were also eligible for the trial.

To avoid methodologic confounding, studies in which the investigational group received other treatments were eligible provided that the control group also received the same treatment or care. Excluded studies were those that focused on burns, dental or jaw treatment, bone fractures, orthopedic injections, plastic surgery, or those that used homologous/allogenic PRP procedures, lysates, freezing or freeze-dried techniques to produce PRP "fibrin glue." Wound healing parameters (e.g., wound area reduction, healing rate, comparisons of clinically significant healing events) used as outcome measures, were reviewed unadjusted or adjusted for other covariates and factors using both baseline and final outcomes as well as repeated measures statistics.

Sources used to obtain studies included the Cochrane Library, Scopus, CINAHL, Pub Med database as well as the clinicaltrial.gov database, using specific search terms. Study quality was assessed using a method reported by Downs and Black (modified by Carter et al.) that evaluated quality of study data reporting, the generalizability of the study, the potential for bias and confounding, and the power of the study to discriminate the effect sizes of the outcomes.

Outcomes were categorized by type, and for each one the pre-treatment and post-treatment numbers, median, or mean values were extracted. Numbers needed to treat (NNT) were calculated and, in cases where protocol analyses were used, the data was updated to reflect an intent-to-treat (ITT) analysis. A fixed-effect model was used to calculate the 95% confidence interval and P values, but if inconsistencies arose, a random effects model was employed. The GRADE classification system was used to compare PRP treatments against standard care treatments. Statistical pooling was carried out on studies that had high homogeneity on: (1) complete wound healing; (2) superficial infection; and (3) reduction in pain, and RCTs were pooled separately from other comparative studies. Statistical heterogeneity was assessed using the I^2 (inconsistency) statistic.

Based on the eligibility criteria, 21 studies (which consisted of 12 RCTs, three cohort studies, five comparative studies, and one retrospective analysis) as well as three systematic reviews were identified and used (qualitative synthesis). After further refinement of the studies, the systematic review revealed the following:

- Four RCTs were found and based on tools used to assess quality, they were all found to have serious limitations (Driver et al. 2006; Friese et al. 2007; Anitua et al. 2008; Saldalamacchia et al. 2004); of these, two were statistically significant for complete wound healing and improved healing time in patients treated with PRP compared to patients treated with saline gel or no topical treatment (Driver et al. 2006; Friese et al. 2007).
- Two RCT studies showed statistically significant differences in wound size reduction in patients receiving PRP compared to subjects who received saline gauze or no topical treatment (Anitua et al. 2008; Saldalamacchia et al. 2004). However, these studies did not report any correlation between wound size reduction and the patients' ability to return to previous function or resumption of normal activities.
- Using propensity scores, a non-RCT comparative study showed that platelet releasate was more effective than standard care in the treatment of diabetic foot ulcers (1.14-1.59) (Margolis et al. 2001).

- A historical cohort study showed that PRP patients required significantly fewer days to complete healing compared to patients in the control group treated with hyaluronic acid-dressings (Mazzucco 2004).

Meta-analyses were also performed based on research design, type of wound (e.g., chronic versus acute), and outcomes (e.g., complete healing, pain reduction, reduction in infection rate). The first meta-analysis found four RCTs that met their criteria for evaluation of chronic healed wounds (Anitua et al. 2007; Driver et al. 2006; Friese et al. 2007; Saldalamacchia et al. 2004). No evidence of significant heterogeneity was noted amongst the studies. Of the four studies, two failed to reveal any statistical difference between patients receiving PRP treatment compared to patients that received saline gel or no topical treatment. When assessing the four studies using a fixed-effect model, the results revealed findings that were significantly in favor of PRP therapy compared to control therapies of saline gauze, saline gel, or not topical treatment ($Z = 2.54$, $P = 0.01$). The authors indicate that this was due to the statistical weight of one study which was presented at a medical conference but was not published as a peer -reviewed article. A meta-analysis for RCTs in acute wounds with primary closure was not performed because only two studies were found.

Another meta-analysis, using a random-effects model was performed to evaluate reduction in infection in acute wounds. The researchers found two articles that met their criteria (Everts et al. 2006; Trowbridge et al. 2005). Results revealed that superficial infections in acute wounds with primary closure was favorable, but were not statistically significant when compared to no topical treatment ($Z = 1.42$, $P = 0.16$).

The final meta-analysis, again using the random effects model, was performed to evaluate acute wounds with primary closure for postoperative pain (Yoo et al. 2008: Buchwald et al. 2008; Englert et al. 2004). Study findings again revealed that the results were in favor of PRP therapy, but were not statistically significant when compared to saline spray or topical treatment ($Z = 0.90$, $P = 0.37$).

Martinez-Zapata MJ, Marti-Caarvajal A, Sola I, Bolivar I, et al. Efficacy and safety of the use of autologous plasma rich in platelets for tissue regeneration: a systematic review. Transfusion. 2009;49(1):44-56.

Using data sources such as MEDLINE, EMBASE, Cochrane registry of controlled trials, and the Science Citation Index, Martinez-Zapata and associates performed a systematic review to determine the safety and tissue regeneration ability of platelet-rich products. Peer-reviewed publications from 1945 to 2006 were reviewed. Inclusion criteria included RCTs that assessed the safety and/or efficacy of PRP for healing and regeneration of hard and soft tissues in any and all medical or surgical procedures. A random-effects model was used by the authors to calculate risk ratios for binary outcomes, and sensitivity analysis was performed if a high degree of heterogeneity was noted amongst the studies. Though 20 RCTs met the inclusion criteria of the study, only seven studies (six parallel designs and one crossover design) addressed the use of PRP in cutaneous ulcers, and only two studies (one parallel and one split design) addressed the use of PRP in surgical wounds.

In studies that evaluated PRP use in patients with cutaneous wounds, Jadad scores were used to assess quality: three studies were considered high quality, three studies were of moderate quality and one study was low quality. Four of the RCTs included patients with chronic ulcers of different etiologies, two studies addressed patients with chronic venous ulcers, and one study addressed patients with diabetic foot ulcers. Six of the seven studies used "complete ulcer epithelialization" as an outcome (the other study used a different definition for healing); combining these six studies resulted in a total of 122 patients in the intervention group and 105 patients in the control group (Knighton et al. 1990; Krupski et al. 1991; Stacey et al. 2000; Senet et al. 2003; Weed et al. 2004; Driver et al. 2006). Results of these combined studies revealed that complete ulcer epithelialization was not statistically significant between the intervention group and the control group (relative risk [RR], 1.40, range 0.85-2.31). Because of the high degree of heterogeneity found between studies (I^2 = 56.8%), a sensitivity analysis was performed, and results were similar to the principle analysis which revealed no statistically significant difference between the two groups (RR, 1.23, range 0.90 - 1.41).

Similarly, the authors found two studies that evaluated the use of PRP in patients with surgical wounds (Powell et al. 2001; Englert et al. 2005). Both studies acknowledged only one treatment session with PRP therapy, and based on Jadad quality scores, both studies were considered of low quality. Outcomes for this group of studies included pain, swelling and redness. Results of the analysis revealed that though the experimental group had better relief in pain, redness and swelling compared to the control group, the degree of improvement was not statistically significant.

The authors concluded that in the treatment of skin ulcers PRP can increase the percentage of recovery but not statistically significantly, and for the treatment of surgical wounds, there was not a statistically significant difference in the outcomes (e.g., pain, redness, swelling, etc.) when compared to the control group.

Villela DL, Santos VL. Evidence on the use of platelet-rich plasma for diabetic ulcer: a systematic review. Growth Factors. Apr 2010;28(2):111-6.

Villela and Santos performed a systematic review to evaluate the use of PRP for the topical treatment of chronic diabetic leg ulcers. Using procedures adopted by the Cochrane Collaborative, articles were retrieved from the following sources: Cochrane, Lilacs, CINAHL, EMBASE, and the Pub Med databases, using July of 2008 as an ending date. Specific inclusion criteria (e.g., clinical trials, complete articles, articles from national and international journals) as well as exclusion criteria (e.g., abstracts, studies using platelet-poor-plasma in combination with PRP; studies using a recombinant or single growth factor) were used in the retrieval of articles. Also specific search terms were used. To evaluate the study quality and evidence, the authors used the scale to assess the grade of recommendation and level of evidence (SGRLE) and the scale to assess control of variables (SACV). The authors acknowledged that there was no scale to assess the intrinsic and extrinsic variables that interfere with chronic wound healing. The Jadad (Oxford) scale was used to assess study quality in cases where RCTs were evaluated. Meta-analysis was performed according to the classification of the results, and both fixed-effects as well as random-effects models were used, depending on the degree of heterogeneity between studies.

There were 18 studies found that met criteria; seven were RCTs and three were cross-sectional clinical studies. When looking at study quality based on the three scales, collectively they were moderate. Only four studies were methodologically similar (Driver et al. 2006; Knighton et al. 1990; Holloway et al. 1993; Steed et al. 1992). A meta-analysis of these four studies was performed. When graphing the four studies individually on a Forest plot, two studies (Holloway et al. 1993; Knighton et al. 1990) reported the best outcome for the treatment group (80% and 81% had healed wounds; CI 2.05-48.5 and 3.65-150 respectively), while the other two studies (Driver et al. 2006; Steed et al. 1992) failed to reveal a difference between the control and treatment group (CI 0.78-10.57 and 0.83-186 respectively). When the four studies were analyzed together, it revealed a trend towards the occurrence of healing and it remained higher in the PRP group compared to the control group (CI 2.94- 20.31). These findings were replicated in both the fixed effect as well as the random effects models. After reviewing results the authors did acknowledge that it is practically impossible to establish a reference value of platelet concentration in PRP necessary to produce healing because each study reported different methods of preparation and concentrations of PRP.

In conclusion the authors note that there was scientific evidence regarding favorable outcomes when using PRP in the treatment of diabetic ulcers, but this is tempered by the knowledge that all studies used different preparations of PRP.

Prospective Studies

A number of prospective studies were identified that evaluated the use of PRP in patients with chronic wounds. These include RCTs (Table 2), as well as other types of prospective studies (Table 3). A number of parameters are captured in the analysis. Most of these prospective studies were randomized, double blind, placebo controlled studies (N = 9), though some prospective trials were open-label trials without control groups. The number of participants in these studies ranged from 13 to 97.

Randomized Clinical Trials

There were nine RCTs identified that addressed the use of PRP in patients with chronic wounds. The primary outcome of interest in these studies was complete wound healing, which was defined as documentation of 100% epithelialization of the wound confirmed by inspection, photography, tracings or planimetry, which is a three dimensional measurement of the wound.

Driver VR, Hanft J, Fylling CP. Beriou JM. A Prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy/Wound Manage. 2006;52(6):68-87.

The objective of this study was to evaluate the safety and incidence of complete wound healing as well as wound recidivism rates among healed wounds in the treatment of non-healing diabetic foot ulcers. To be eligible for the study, participants must have type I or type II diabetes, be between the ages of 18 and 95, and must have an ulcer that has lasted for at least four weeks. A total of 72 patients met the inclusion criteria, including 40 participants in the intervention group (PRP gel) and 32 participants in the control group (saline gel). The mean age in intervention group was 56.4 years, while the mean age in the control group 57.5 years (reported as not statistically significant). The percentage of males in the intervention and control groups were 80%/81.4 respectively (reported as not statistically significant). Patients received treatment twice weekly, either PRP gel, or saline gel. An Intent-to-Treat Analysis (ITT) was performed, and of the 72 participants, 13 of 40 patients (32.5%) in the PRP gel and nine of 32 patients (28.1%) in the control group had completely healed wounds after 12 weeks (P = 0.79).

Because the authors felt that the ITT analysis results did not reflect previous clinical outcomes, an independent audit was performed. This resulted in the elimination of 32 participants due to protocol violations and failure to complete treatment. The final analysis was based on 19 patients in intervention group and 21 patients in control group. Based on this new per-protocol analysis, 13 of 19 (68.4%) patients in PRP gel and nine of 21 (42.9%) patients in the control group had complete healing (P = 0.125). As part of a post-hoc analysis, results were reanalyzed based on wound size. After adjustment, more patients in the PRP group had complete healing (81.3%) compared to patients in the control group (42.1%), respectively (P = 0.036). When looking at the 40 patients in the per-protocol database subset one patient in the PRP gel group had a wound that reopened, while in the saline gel group there were no reopened wounds (not statistically significant). No treatment-related serious adverse events were noted during the study. The authors concluded that PRP gel is safe for the treatment of non-healing diabetic ulcers, and that in the most common size of diabetic ulcers (< 7.0 cm^2 in area and < 2cm^3 in volume), PRP gel-treated wounds also were significantly more likely to heal than control gel treated wounds.

Holloway GA, Steed DL. DeMarco MJ, Masumoto T, et al. A randomized, controlled, multicenter, dose response trial of activated platelet supernatant, topical CT-102 in chronic non-healing, diabetic wounds. Wounds. 1993;5(4):198-206.

The purpose of this study was to evaluate the safety and efficacy of homologous platelet releasate. Patients eligible for study were diabetics with chronic, non-healing wounds that persisted for a minimum of eight weeks. The extent of wounds were graded from Grade 1 (partial thickness ulcer involving only the dermis and epidermis) to Grade 6 (full-thickness ulcer involving bone, ligament, joint and had gangrene in the surrounding tissue) based on wound characteristics. The study used a functional assessment tool that looked at the degree of epithelialization, drainage, and the need for dressing change. These parameters ranged from Level 1 (< 100% epithelialization with drainage/need to change dressing) to Level 4 (100% epithelialization no drainage/no need to change dressing). In the study, 70 participants were randomized to either placebo group or to one of three dilution groups-0.01, 0.1, or 0.033, to be received once a day.

Baseline characteristics of patients and wounds failed to show any differences in mean age of patients between the three dilutions and placebo group. Mean ages ranged from 59 and 62 between the four groups. There was no significant difference between treatment groups in regard to wound severity scores at baseline. Results of the study revealed that wound healing was higher in all groups of platelet-derived wound healing factor (PDWHF) dilution compared to the control group; 29% had complete healing in the control group, while in the PDWHF group, healing occurred in 80%, 62%, and 52% in the 0.01, 0.033 and 0.1 dilution groups respectively (P = 0.02). In terms of healing, no statistical difference was noted among the drug solutions. The median time for complete healing in the PDWHF group was 140 days, but the median time for complete healing in the control group could not be determined since less than half of the patients in this group healed by the end of the study. The authors concluded that PDWHF was more effective than placebo in healing diabetic wounds.

Knighton DR, Ciresi K, Fiegel VD, Schumerth S, Butler E, Cerra F. Stimulation of repair in chronic, non-healing, cutaneous ulcers using platelet-derived wound healing formula. Surg Gynecol Obstet. Jan 1990;1701(1):56-60.

The purpose of this crossover study was to test whether or not PDWHF accelerates repair of chronic non-healing cutaneous ulcers. In this study, 32 patients with chronic, non-healing wounds of the lower extremities were randomized to eight weeks of therapy with either PDWHF or placebo (platelet-buffered solution). Total Wound Severity Scores (TWSS) were used to classify severity of wounds based on clinical as well as anatomic findings, along with measured wound and patient variables. Patients had to have a wound for at least eight weeks to be included in the study. Enrollees were placed on a twice-daily wound dressing protocol. After eight weeks, 17 out of 21 wounds (81% of patients) in PDWHF treatment group achieved epithelialization compared to two of 13 (15% of patients) in the control group ($P < 0.0001$). After crossover to treatment with PDWHF, all of the patients in the control group had epithelialization in an average of 7.1 weeks. The authors concluded that there is a significant increase in the rate of epithelialization of the wounds in patients treated with PDWHF.

Krupski WC, Reilly LM, Perez S, Moss KM, Crombleholme PA, Rapp JH. A prospective randomized trial of autologous platelet-derived wound healing factors for treatment of chronic non-healing wounds: A preliminary report. J Vasc Surg. 1991;14:526-36.

The purpose of this study was to assess the ability of platelet factors to facilitate healing of chronic wounds. Participants included 18 patients with 26 lower extremity wounds that were refractory to conventional therapy. Wound etiology included diabetes (78% of patients), peripheral vascular disease (72% of patients), as well as venous disease (28% of patients). The treatment group (n = 10, with 17 wounds) received topical PDWHF while the control group (n = 8, with 9 wounds) received conventional therapy for type of wound. Both groups received standard surgical and supportive care. To be eligible for the study, patients needed to have at least one chronic non-healing wound of eight weeks duration or longer. Wounds were graded on a scale from one (e.g., relatively superficial robust wound) to six (e.g., deeper more complicated wound) based on wound characteristics. Participants ranged in age from 57 to 75, and on average, wounds were present for 5.5 months prior to enrollment in the study.

There were no significant differences in demographics or laboratory values between the two treatment groups. The average duration of therapy was 10.1 +/- 2.7 weeks (median 12, mode 12). Participants were to receive PDWHF or placebo solution every 12 hours. Results of the study revealed that three of nine (33%) in the control group had complete healing, while four of 17 (24%) in the PDWHF had complete healing. No significant difference was observed in comparing either wounds healed or patients healed. The author concluded that PDWHF provides no additional benefit over traditional therapy.

Saad Setta H, Elshahat A, Elsherbiny K, Massoud K, Safe I. Platelet-rich plasma versus platelet-poor plasma in the management of chronic diabetic foot ulcers: a comparative study. Int Wound J. Jun 2011;8(3):307-12.

The aim of this study was to investigate the efficiency of platelet releasate on the healing of chronic wounds. Eligible patients included type I or type II diabetics between 40 and 60 years of age with a history of non-healing diabetic ulcers of at least 12 weeks duration. Twenty-four patients participated in the study and they were equally enrolled in the PRP (platelet-rich plasma) group and PPP (platelet-poor plasma) group. Participants received PRP or PPP treatments twice weekly. Results of the study revealed that the incidence of wound healing was the same in both groups (100%); though the mean healing time for the PRP group was 11.5 weeks, while healing time in the PPP group was 17 weeks ($P < 0.005$). No mention was made about recurrence of ulcers after healing. The authors concluded that PRP promotes and accelerates healing of chronic diabetic foot ulcers.

Stacey MC, Mata SD, Trengove NJ, Mather CA. Randomised double-blind placebo controlled trial of topical autologous platelet lysate in venous ulcer healing. Eur J Vasc Endovasc Surg. Sep 2000;20(3):296-301.

The purpose of this study was to determine if topical platelet lysate sped up the healing process in patients with chronic venous ulcers. A total of 86 patients were randomized to either the experimental group (n = 42) or the placebo group (n = 44) to receive either platelet lysate or placebo buffer solution twice a week. Patient characteristics as well as age and gender distribution were similar between both groups. Results of the study revealed that 34 of 44 subjects (77%) in the placebo group had complete healing, while 33 of 42 subjects (79%) in the intervention group had complete healing. The authors noted no difference between the two groups in terms of healing. The authors concluded that the use of topical platelet lysate had no significant influence on venous ulcer healing.

Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. Plast Reconstr Surg. Jun 2006;117(7 Suppl):143S-149S.

In this analysis, Steed combined data from four previous RCT studies in an attempt to determine the safety and efficacy of topically applied gel, either rhPDGF-BB30µg/g or rhPDGF-BB100µg/g, compared to placebo gel or good ulcer care. All participants received the standardized protocol of good ulcer care. Enrollment included 922 men and women, ranging in age from 23 to 93 years (median age 59) with either type I or type II diabetes. In the four trials the combined numbers of patients in each treatment group were as follows: rhPDGF-BB30µg/g , n = 193; rhPDGF-BB100µg/g, n = 285; placebo gel, n = 254; good ulcer care, n = 190. Baseline characteristics of patients were similar between all four groups within and across studies. Of the 922 patients treated, 874 (95%) had baseline ulcer areas that were less than or equal to 10 cm^2. As per protocol, patients received treatments daily. Results of the study revealed that complete healing was higher in the rhPDGF-BB100µg/g group compared to placebo gel treatment (50% versus 36%, P = 0.007), and results were similar in patients with baseline ulcer areas that were less than or equal to 10 cm^2 in all four studies.

The first of the four studies was a phase II trial that assessed the efficacy of rhPDGF-BB30µg/g. It revealed a healing rate of 48% for patients treated with rhPDGF-BB30µg/g compared to a healing rate of 25% for those treated with placebo gel. The second study was a phase III trial looking at efficacy of rhPDGF-BB at 30µg/g and 100µg/g dosages, and it revealed a healing rate of 50% for patients treated with rhPDGF-BB100µg/g, 36% for patients receiving rhPDGF-BB30µg/g and those receiving placebo gel. The third study compared placebo gel with that of good ulcer care alone and revealed the overall incidence of complete healing in all patients was 44% for patients receiving rhPDGF-BB100µg/g, compared to 36% for those receiving placebo gel and 22% for those receiving good ulcer care alone. The final study assessed resource utilization and found that the incidence of complete ulcer healing in the rhPDGF-BB100µg/g group was 36% and that for the good ulcer care group alone was 32%, but the authors did not report if the findings were statistically significant.

Steed DL, Goslen JB, Holloway GA, Malone JM, Bunt TJ, Webster MW. Randomized prospective double-blind trial in healing chronic diabetic foot ulcers. Diabetes Care. 1992;15(11):1598-1604.

The purpose of this study was to determine the effect of topically applied purified platelet releasate (also known as PDWHF) on the healing of chronic diabetic neurotrophic foot ulcers. In order to be eligible for the study, the diabetic patients needed to have a non-healing neurotrophic ulcer on the lower extremity for at least eight weeks despite standard therapy consisting of antibiotics and protective devices, resting the involved region and debridement of necrotic tissue. Length, wide, and depth of ulcers were measured, and photos were taken. Ulcer dressings were changed every 12 hours and either PDWHF or placebo solution was applied. The study consisted of 13 participants (nine males, four females), seven in PDWHF group ranging in age from 39-75 (mean age of 59), and six in the control group ranging in age from 41-74 (mean age of 54). Patients in the control group received standard therapy along with placebo (normal saline), while patients in intervention group received standard therapy along with PDWHF. Analysis of demographic data revealed that baseline characteristics were the similar between both groups except the treatment group had diabetes longer than the control group (26 years versus 10 years). Results of the study revealed that one of six (17%) ulcers healed by week 20 in the control group, while five of seven ulcers healed in the PDWHF group (71%) within 15 weeks. The authors concluded that PDWHF accelerated wound closure in diabetic leg ulcers when administered as part of a comprehensive program for the healing of chronic wounds.

Weed B, Davis MDP, Felty CL, Liedl DA, et al. Autologous platelet lysate product versus placebo in patients with chronic leg ulcerations: a pilot study using a randomized, double-blind, placebo-controlled trial. Wounds. 2004;16(9):1-14.

The objective of this study was to assess the ability of autologous platelet lysate to facilitate healing of chronic cutaneous ulcers. In this study (N = 26), 15 patients received autologous platelet lysate product mixed with collagen (treatment group) while 11 patients received PPP mixed with collagen (placebo group). Treatments were applied twice daily for 12 weeks. After the 12 weeks, there was a washout period of two weeks, and patients whose ulcers had not healed were then assigned to receive whichever treatment they had not received in the previous 12 weeks. Results of the study revealed that during the first 12 weeks, in the treatment group, nine of 15 (60%) patients healed, while four of 11 (36%) in the control group healed. There was not a statistically significant difference between the proportion healed wounds in these two groups at 12 weeks (P = 0.68). After a two-week washout period, in the treatment group two (29%) of the patients healed, while two (33%) of the patients in the control group healed.

There was not a statistically significant difference between the proportion healed in these two groups at the end of the second 12 week period (P = 0.99). Throughout the study, 11 patients (42%) healed with platelet lysate, six (23%) healed with placebo treatment, and nine (35%) failed to heal. In the analysis using both time periods, there was not a statistical difference between treatment groups in the proportion of wounds healed (P = 0.31). The authors concluded that autologous platelet lysate product in addition to collagen did not accelerate the rate of wound healing or significantly decrease wound size compared to platelet-poor plasma with collagen.

Other Prospective Studies

A number of other prospective studies with a limited number of participants have been performed evaluating the use of PRP in chronic wounds (Table 3).

One was an open-label trial involving 13 patients with a total of 14 venous leg wounds and diabetic foot ulcers (Gurgen 2008). After one month of PRP treatment, only one wound was completely healed. And though there was a reduction in size, the remaining 13 wounds had not healed. Over the next ten months, an additional seven ulcers healed. By the end of the study almost a year later 35% of the wounds had not healed. A second prospective study involved the use of autologous PDGF in 24 patients with a total of 33 chronic non-healing wound in the lower extremities (McAleer et al. 2006). Wounds had a variety of etiologies including venous stasis ulcers, decubitus ulcers, arterial insufficiency ulceration, ulcers due to diabetic traumatic events, and diabetic ulcers with neuropathic pathology. By the end of the study ten months later, 20 wounds exhibited complete epithelialization, eight wounds showed reduction in size with no healing, and the remaining five wounds showed no improvement. One final prospective study evaluated the use of autologous platelet-rich fibrin matrix in 21 patients with non-healing lower extremity ulcers (O'Connell et al. 2008). In the study 12 patients with 17 venous ulcers and nine patients with 13 non-venous ulcers were treated with platelet-rich fibrin matrix along with the appropriate standard wound care. By the conclusion of the study, a little more than half of patients with venous leg ulcers treated with autologous platelet-rich fibrin, and less than half of patients with non-venous ulcers treated with autologous platelet-rich fibrin had complete closure.

Retrospective Studies

A number of retrospective studies were also found. Some were comparative in nature and contained a control group while others studies had a limited number of participants (Table 4). Steenvoorde and associates conducted a study designed to determine if autologous platelet-rich fibrin could improve the healing rate of hard to heal wounds, and included patients with diabetic ulcers, venous ulcers, traumatic ulcers, radiotherapy ulcers, pressure ulcers, ischemic ulcers, as well as mixed etiology ulcers (Steenvoorde et al. 2008). Outcomes of interest included full wound closure with no recurrence, reduction in wound diameters, and occurrence of adverse events. Participants included twelve patients with 13 wounds. By the end of the study eight (62%) of the wounds had closed with no recurrence, the remainder either did not heal completely or did not show a reduction in size.

Keyser and associates was interested in determining complete wound healing and limb salvage rates in patients with chronic diabetic wounds (Keyser et al. 1993). The study enrolled 54 diabetic patients who had a total of 86 chronic wounds and participated in a comprehensive program that consisted of a number of treatment modalities including antibiotic therapy, patient education, protective devices, non-weight bearing, as well as a topical growth factor solution consisting of PDWHFs. Results of the study revealed that 88% of all wounds healed within 16 weeks, and of all the wounds recommended for amputation, 93% were able to be salvaged. But of the patients with healed wounds, six patients with six wounds (7%) had early recurrence of their wound with resumption of weight bearing, and ten wounds in nine patients failed to heal in the six-month follow-up period.

In another retrospective study, Mazzucco and associates' goal was to determine if dressing non-healing skin lesions with autologous platelet gel would induce acceleration of tissue regeneration (Mazzucco et al. 2004). Patients with dehiscent sternal wounds (Group 1) and full-thickness Stage III or IV necrotic skin wounds (Group 2) were included in the review. Autologous platelet gel was used as the intervention in the experimental cohort in both groups, and controls for both groups were treated with conventional therapy for the type of wound. The study included 53 participants, 22 in Group 1 (10 treated and 12 controls) and 31 participants in Group 2 (17 treated and 14 controls). Patients treated with autologous platelet gel were retrospectively compared to patients with similar lesions but underwent conventional treatment. Demographics and clinical characteristics were similar for each group. Study results revealed that in patients with dehiscent sternal wounds (Group 1), those treated with autologous platelet gel achieved 100% healing faster, and had fewer hospital days compared to those that received conventional therapy. In patients with full-thickness Stage III or IV necrotic skin wounds (Group 2), time required to have surgery was shorter and no local recurrence of wounds occurred after surgery in patients receiving autologous platelet gel compared to patients in the control group.

Another retrospective study was a 4-year multicenter study that looked at data on 3830 patients with chronic wounds, consisting of ulcers related to diabetes, venous insufficiency, pressure, PVD, autoimmune disease, wounds from surgical procedures, spider bites or traumatic injury (Glover et al. 1997). Of that number, 1,019 were included in the control group (comprehensive wound care alone), and 2,811 were included in the intervention group (comprehensive wound care and platelet releasate). Results of the study demonstrated that patients in the comprehensive wound care who also received platelet releasate had higher healing rates ($P < 0.001$), and had a lower amputation rate ($P < 0.0005$) than patients that received comprehensive wound care alone.

Margolis and associates performed two retrospective cohort study based on a database maintained by Curative Health Services that contained information on over 120,000 chronic wounds. The first study looked at the effect of platelet releasate (PR) as a treatment option in patients with diabetic neuropathic foot ulcers (Margolis et al. 2001) In this study, almost 26, 000 diabetic patients were identified and divided into two groups: those that had received PR by the 12^{th} week of treatment (n = 6,252), and those who had not received PR by the 12th week of treatment (n = 20,347). Patient characteristics such as gender, age, wound area, wound grade, and wound volume were captured. A logistic regression model using propensity scores was developed to minimize selection bias. This resulted in 14 covariates that were included in the model. Patients were stratified into quintiles based on these propensity scores. They ranged from Group 1 which consisted of patients least likely to receive PR to Group 5 which consisted of patients most likely to receive PR. Quintile specific healing rates for PR and non PR groups were calculated. According to the author, treatment groups were well balanced for risk factors. Results of the study revealed that patients treated with PR were more likely to have larger, older, higher grade wounds, and were more likely to heal than patients not treated with PR (the relative risk for healing increased from Group 1 to Group 5). This finding was duplicated in all five quintiles.

The second retrospective cohort study performed by Margolis and associates was to estimate the effectiveness of rhPDGF in actual clinical practice in patients with diabetic neuropathic foot ulcers (Margolis et al. 2005). Again using a database maintained by Curative Health Services that contained information on over 120,000 chronic wounds, a subset of patients with diabetic neuropathic foot ulcers was identified (n = 24,898), and of this number 2,394 (9.6%) were treated with rhPDGF. Propensity scores were used to statistically model treatment selection to minimize selection bias attributable due to observed covariates. Patients were stratified into quintiles based on the distribution of propensity scores which varied between those least likely to receive rhPDGF (Group 1) and those most likely to receive rhPDGF (Group 5). Quintile-specific healing and amputation rates for the rhPDGF and non-rhPDGF were calculated, and the effectiveness of rhPDGF was assessed by calculating the quintile-specific relative risk of healing for those who received rhPDGF. Results of the study overall revealed that patients that received rhPDGF were more likely to heal than patients that did not received rhPDGF, and patients that received rhPDGF were less likely to have amputations compared to those that did not receive rhPDGF.

The final retrospective study was performed by Mazzucco and associates, and it's aim was to determine if dressing non-healing skin lesions with autologous platelet gel would induce acceleration of tissue regeneration (Mazzucco et al. 2004). In this study, data on patients with dehiscent sternal wounds (Group 1) and full-thickness Stage III or IV necrotic skin wounds (Group 2) was reviewed. Autologous platelet gel was used as the intervention in the experimental cohort in both groups, and controls for both groups were treated with conventional therapy for the type of wound. The study included 53 participants, 22 in Group 1 (10 treated and 12 controls) and 31 participants in Group 2 (17 treated and 14 controls). Patients treated with autologous platelet gel were retrospectively compared to patients with similar lesions but underwent conventional treatment. Demographics and clinical characteristics were similar for each group. Results of the study revealed that in patients with dehiscent sternal wounds (Group 1), those treated with autologous platelet gel achieved 100% healing in nearly half the time (median, 3.5 versus 6.0 weeks; P = 0.0002) and had fewer hospital days (median, 31.5 versus 52.5) compared to those that received conventional therapy. No recurrences of wounds or complications were noted in the platelet gel group. But as noted before, the study of PRP's effect on acute wounds was not within the scope of the NCD. In patients with full-thickness Stage III or IV necrotic skin wounds (Group 2), time required to have surgery was significantly shorter (15.0 weeks versus 35.5 weeks; P < 0.0001) and no local recurrence of wounds occurred after surgery. The author concluded that patients with both acute and chronic non-healing wounds showed substantial improvement with autologous platelet gel compared to patients treated with conventional therapy.

4. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

A MEDCAC meeting was not convened on this topic.

5. Evidence-based Guidelines

A summary clinical algorithm for a guideline by the Association for the Advancement of Wound Care was found during a search of the National Guideline Clearinghouse database. The algorithm, titled "Summary algorithm for venous ulcer care with annotations of available evidence" briefly notes the use of biologic dressings for wounds at least 30 days old as well as the use of PDGF. However, an evidence strength rating of "C" was assigned to each. This rating means that at least one of the following is lacking: results from a controlled trial, results of at least two case series or descriptive studies or a cohort study in humans, or expert opinion.

In 2006, the Wound Healing Society published evidence-based guidelines to demonstrate the best care of chronic wounds. The guidelines were presented by type of chronic wound (diabetic ulcers, venous ulcers, pressure ulcers, and arterial insufficiency ulcers). Only the venous ulcer guideline addressed a PRP-type of treatment and noted that this treatment has "yet to be shown to demonstrate sufficient statistically significant results or effectiveness to recommend" its use.

6. Professional Society Position Statements

An internet search failed to locate any professional society position statements exclusively concerning autologous PRP in the treatment of chronic wounds. It is possible that CMS may receive professional society position statements on the proposed decision.

7. Expert Opinion

We may receive expert opinions on the proposed decision during the comment period.

8. Public Comments

CMS uses the initial public comments to inform its proposed decision. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information is redacted and protected and are not made available to the public. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. On the tracking sheet for this NCD, CMS requested public comments on the evidence speaking to the health outcomes attributable to the use of PRP products in the treatment of chronic non-healing pressure ulcers, venous ulcers and diabetic foot ulcers. CMS also encouraged the submission of comments that would pertain to clinical studies falling under the Coverage with Evidence Development (CED) paradigm.

Initial Comment Period

During the initial 30-day public comment period (11/09/2011 – 12/08/2011), CMS received a total of 126 comments. Most comments were generally in favor of coverage, however a few comments strongly opposed coverage, and one expressed no clear indication for coverage.

CMS received a total of 15 comments that referred to evidence that were either already received by the requestor or considered later in the analysis. Two of these comments were non-supportive of coverage stating that there is insufficient clinical data demonstrating the safety and efficacy of PRP gel for treating chronic cutaneous ulcers.

CMS received a number of comments from physicians, surgeons and perfusionists. One perfusionist expressed opposition of national coverage and emphasized that too much money is spent on PRP with no substantial scientific evidence of its safety.

CMS received a number of comments from other individuals within the healthcare industry, such as nurses, podiatrists, physical therapists, professors, hospital administrators, professional societies, healthcare insurers, etc. CMS also received comments from representatives of manufacturing companies and other businesses and consulting firms. These commenters include lawyers, sales representatives, consultants and executives. One commenter suggested that CED is better than national non-coverage.

CMS received seven comments from the various public organizations and patients. Many commenters stated that PRP treatment yielded positive results such as improved wound healing time, less pain after surgery, and in one instance avoided amputation.

All comments that were submitted via CMS coverage website may be viewed by using the following link:
http://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=260

VIII. CMS Analysis

National Coverage Determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item of service is covered nationally by Medicare (§1869 (f)(1)(B) of the Act).

In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, §1862(a)(1) of the Act in part states that, with limited exceptions, no payment may be made under Part A or part B for any expenses incurred for items or services:

- which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)) or
- in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section. ((§1862(a)(1)(E)).

Section 1142 of the Act describes the authority of the AHRQ. Under section 1142, research may be conducted and supported on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically

Section 1862(a)(1)(E) allows Medicare to cover under CED certain items or services where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. For your convenience, the 2006 CED guidance document is available at www.cms.gov/determinationprocess/downloads/ced.pdf.

A. §1862(a)(1)(A) Analysis

1. Question:

Is the evidence adequate to conclude that Medicare beneficiaries who have chronic non-healing diabetic, venous and/or pressure wounds that receive PRP therapy experience clinically significant health outcomes as indicated by at least one of the following:

a. Complete wound healing?
b. Ability to return to previous function and resumption of normal activities?

In analyzing the evidence, CMS focused on evidence that PRP provides patient-centered health benefits (e.g. complete healing, less recurrent wounds, improved quality of life) in patients with chronic pressure, venous or diabetic wounds.

Increased healing trajectory is often mentioned in the medical literature as a surrogate for complete wound healing, especially in acute wounds (Carter et al. 2011). It also has been noted that the use of a dynamic healing trajectory or healing time curve may allow the prediction of healing of an individual wound (Robson, Hill, Woodshe, and Steed 2000). But because the healing process differs between acute and chronic wounds, the use of healing trajectory may not be appropriate for chronic wounds. Studies that emphasize percentage of surface wound healings are also often touted as predictable or reliable indicators for healing. But acute wounds that often start off healing well, can stop in mid-course and become chronic non-healing wounds. Though healing trajectory and percentage of surface wound reduction might be useful efficacy endpoints, as noted in the questions and outcomes section, CMS underscores the importance of complete wound healing or the ability to return to previous function and resumption of normal activities when considering patient-centered health outcomes.

Systematic Reviews/Meta-Analysis

Carter MJ, Fylling CP, Li WW, de Leon JM, et al. Analysis of run-in and treatment data in a wound outcomes registry: clinical impact of topical platelet -rich plasma gel on healing trajectory. Int Wound J. Dec 2011;8(6)638-50.

Using RCTs and comparative group studies, Carter et al. performed a systematic review and meta-analysis on the use of plasma rich plasma gel in wound healing. Based on their analysis, they felt that the studies confirmed that PRP was effective in healing wounds. But in assessing the study, a number of concerns were identified:

- The author acknowledged that one limitation of the study was the fact that there were so many citations evaluating the impact of PRP and many methods and definitions for determining and measuring wound healing were used.
- The analysis included not only patients with chronic wounds, but also patients with acute wounds, including open surgical wounds treated with PRP prior to closing and opening. (Almdahl et al. 2011; Buchwald et al. 2008; Englert et al. 2008; Gardner et al. 2007). This NCD specifically addresses the use of PRP in patients with chronic wounds.
- Included in the review were abstracts taken from scientific meetings, posters, and letters to editors (Friese et al. 2007; Saldalamacchia et al. 2004). They were used in the systematic review as well as the meta-analysis. The study performed by Friese, which had the highest statistical weight, was not a peer-reviewed study, but a poster presented at conference. These sources do not carry the evidentiary weight needed to determine the relationship between the intervention being discussed (e.g., PRP), and the outcome of interest (e.g., complete wound healing).
- A number of outcome measures other than complete healing were use in this systematic review and meta-analysis, including wound healing trajectory, wound healing velocity and percentage reduction in wound size (Anitua et al. 2007; Carter et al. 2011; Peerbooms et al. 2009). Complete wound healing was the primary outcome of most importance to CMS as stated in our research questions. Because of favorable findings not of primary interest to CMS, results of this systematic review and meta-analysis are not as helpful to CMS in determining its usefulness in our population with chronic wounds.
- This systematic review used Downs and Black reporting method (modified by Carter et al. 2011) to assess study quality. Even if studies were RCTs, this scoring system was used. In assessing quality of studies, the other systematic reviews included in this analysis used either the Jadad-Oxford Quality Scoring System alone (Martinez-Zapata 2009), or a combination of SGRLE system, the SACV system, along with the Jadad Scoring system. No explanation was provided why the Downs and Black scoring system was used as opposed to the more commonly-used Jadad Oxford scoring system. Because of differences in quality measurement tools, this could lead to inconsistency in results, which is a threat to internal validity amongst the studies.
- Based on the quality tool that was used, the four RCTs that evaluated complete wound healing had serious limitations. This could affect the validity of the study.
- In the meta-analysis that evaluated the impact of PRP on chronic wounds, an impact study was used (Anitua et al. 2007). It did not provide sufficient information about population size, event size, risk difference or other parameters to determine the impact of PRP. It would be difficult to perform a statistical analysis and determine if PRP is reasonable and necessary without this information.
- In one of the articles included in the analysis, it initially showed that there was no difference in outcomes between diabetic foot ulcers patients treated with PRP and controls (Driver et al. 2006). But a later analysis was performed because of protocol violations, failure to complete treatment, and because the results were not consistent with previous research studies. This second analysis resulted in 32 (44%) patients being excluded from the analysis. With these patients excluded a per-protocol analysis was performed, and the results then revealed that patients who received PRP gel had a higher healing rate than those who did not get the PRP gel. An intent-to-treat analysis was not followed in this study.
- Two other meta-analyses were performed on acute wounds to determine if pain reduction and decreased rate of superficial infection occurred in patients receiving PRP. The results of both analyses failed to show that patients had better outcomes with PRP products as oppose to controls. Though this information is interesting, it is not helpful in determining the usefulness of PRP in patients with chronic wounds.
- Studies used differing concentrations of PRP, and no attempt was made to standardize or adjust data.

Martinez-Zapata MJ, Marti-Caarvajal A, Sola I, Bolivar I, et al. Efficacy and safety of the use of autologous plasma rich in platelets for tissue regeneration: a systematic review. Transfusion. 2009;49(1):44-56.

Using RCTs, Martinez-Zapata et al. performed a systematic review to determine tissue regeneration among patients with chronic skin ulcers. Results of the study revealed that there was no statistical difference between patients receiving PRP compared to patients in the control group. But as noted by the author there were a number of limitations of the study, including:

- Small sample sizes and large Confidence Intervals in the studies reviewed.
- Primary and secondary outcomes were highly heterogeneous and difficult to measure.
- Study quality was heterogeneous, which could call into question the validity of the study.
- Variation in results due to RCT including chronic ulcers of different etiologies.
- Differing concentrations of PRP preparations used in the studies.

Villela DL, Santos VL. Evidence on the use of platelet-rich plasma for diabetic ulcer: a systematic review. Growth Factors. Apr 2010;28(2):111-6.

Villela and Santos also performed a systematic review to evaluate the use of PRP for the topical treatment of chronic diabetic leg ulcers (Villela & Santos 2010). They concluded that there was sufficient evidence to conclude that the use of PRP for the treatment of diabetic ulcers was better than comparison treatment. The authors acknowledged a number of limitations of the study including:

- Despite the observation of positive outcomes, especially in terms of healing rates that confirm the effectiveness of this approach, the PRP used in the treatment of diabetic ulcers cannot be considered an isolated factor since a multi-professional treatment program for patients was included in all studies analyzed.
- Confounding was not addressed and controlled for.
- Small sample sizes in the studies used.
- In the largest study used in the meta-analysis, groups were not stratified before randomization.
- Not possible to establish a reference value for platelet concentration in these PRP studies for healing purposes, since each study reported different methods of preparataion and concentrations.

In summary, in addition to the limitations listed for each systematic review/meta-analysis, all three studies used different tools to measure study quality. Carter et al. used Downs and Black reporting method, Martinez-Zapata et al. used Jadad Oxford quality tool, and Villela et al. used SGRLE scale, the SACV scale Jadad (Oxford) scale when needed. And though all three meta-analysis used quality tools to assess studies, there was very little agreement in terms of studies which were defined as high quality, moderate quality or low quality studies. All meta-analyses used a fixed effect model; and if a high degree of heterogeneity was found among the studies, a random-effects model was performed. But each study used a different cut-off point to identify heterogeneity. And though the studies did address the issue of wound healing, they did not address other pertinent research questions that CMS is seeking answers on, including durability (non-recurrence), resumption of normal activities and improved quality of life.

Randomized Clinical Trials

Driver VR, Hanft J, Fylling CP. Beriou JM. A Prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy/Wound Manage. 2006;52(6):68–87.

This study evaluated the use of PRP in patients with diabetic foot ulcers. Using an intent to treat analysis based on the 72 patients originally enrolled in the study, the researchers found no difference between the PRP group and the control group (P = 0.79). But a later audit and analysis was performed because the findings of the original study did not reflect previous clinical outcomes. This resulted in the exclusion of 32 participants. A new analysis of the data was performed, after adjusting for wound size. It showed that patients treated with PRP had a higher complete healing rate compared to patients in the control group. Issues of this study include:

- The study excludes ulcers with "challenging presentation" such as those with mild to moderate vascular disease and exposed tendon or bone along with patients who had hyperglycemia and/or inadequate nutritional status. Other studies included patients with severe wounds, including patients with exposed bones and tendons (Knighton et al. 1990, Holloway et al. 1993).
- An intent to treat analysis was not followed.
- A large number of patients (32) were excluded from the study after an audit was performed because results of the study were not consistent with previous studies.
- When analysis was run on the remaining 40 participants, there was no statistical difference between healing in the two groups. But a post-hoc analysis was performed which eliminated wounds greater than seven cm2, (n = 5), then results became statistically significant for the PRP group compared to the control group. Wounds up to 20 cm2 were initially included in the inclusion criteria, but then criteria were relaxed.
- Article states that the size range correlates with the average wound size in multiple published studies, but only listed one study (Margolis et al. 2003). Also when reviewing the study listed, it only mentions mean log wound size, and does not use the parameters (cm2) as mentioned in the Driver article.
- No mitogenic assay was performed to test the potency of the platelet product.

Holloway GA, Steed DL, DeMarco MJ, Masumoto T, et al. A randomized, controlled, multicenter, dose response trial of activated platelet supernatant, topical CT-102 in chronic non-healing, diabetic wounds. Wounds. 1993;5(4):198-206.

The authors of this study concluded that PDWHF was more effective than placebo in healing wounds. But the primary concern of this study was the variation in comparators within the same study. At the beginning of the study, 14 patients were given either 0.01 dilution of CD-102 or a placebo consisting of physiologic normal saline. Later, the study was revised to include two additional dilutions of CT-102 at 0.1 and 0.03, and the placebo solution changed to an isotonic platelet buffer. It is unclear whether the final results were consistent among the study groups due to these changes during the study.

Knighton DR, Ciresi K, Fiegel VD, Schumerth S, Butler E, Cerra F. Stimulation of repair in chronic, non-healing, cutaneous ulcers using platelet-derived wound healing formula. Surg Gynecol Obstet. Jan 1990;1701(1):56-60.

This study demonstrated that patients who received the platelet-derived wound healing formula that was derived from autologous platelets have a higher healing rate compared to patients who received placebo. But concerns of this study include:

- Randomization was not stratified according to diagnostic groups.
- Age, initial wound area and wound location are potential confounders in the study and were not controlled for.
- The two groups were not completely similar; wound size was larger in the control group, while wound duration was longer in the treatment group.
- Study period was only eight weeks. As noted by the authors, if it were longer, more in the control group might have healed.

Krupski WC, Reilly LM, Perez S, Moss KM, Crombleholme PA, Rapp JH. A prospective randomized trial of autologous platelet-derived wound healing factors for treatment of chronic non-healing wounds: A preliminary report. J Vasc Surg. 1991;14:526-36.

The study performed by Krupski et al. showed that there was no difference in the healing rate of chronic wounds between experimental group and control group. The authors noted potential flaws in the study including:

- Randomization was not stratified according to wound origins which could lead to a Type 2 error (no difference between the two groups when there actually is a difference between the two).
- Dissimilarities between the two groups.
- Confounding due to the biological activity of PDWHF, because the potency of PDWHF could vary between both groups.

Saad Setta H, Elshahat A, Elsherbiny K, Massoud K, Safe I. Platelet-rich plasma versus platelet-poor plasma in the management of chronic diabetic foot ulcers: a comparative study. Int Wound J. Jun 2011;8(3):307-12.

This RTC was able to demonstrate that patients who received PRP gel had a higher healing rate than patients that received PPP gel. The main concerns of this study are:

- Participants restricted to patients between age 40 and 60.
- Patients were randomized to either the experimental group or the control group based on even/odd numbering (even number patients were placed in the plasma-poor gel group, while odd number patients were placed in the PRP group). There was no mention of how patients were assigned numbers. This is not a rigorous way of randomizing patients.
- No mitogenic assay was performed to test the potency of the platelet product.

Stacey MC, Mata SD, Trengove NJ, Mather CA. Randomised double-blind placebo controlled trial of topical autologous platelet lysate in venous ulcer healing. Eur J Vasc Endovasc Surg. Sep 2000; 20(3):296-301.

This study assessed the effect of topical platelet lysate on chronic venous ulcers, and showed that PRP had no influence on the healing. The following issues are of concern:

- One potential confounding factor in the design of this study was the lack of data on deep vein reflux and post-thrombotic changes. If there was an uneven distribution of deep vein abnormalities between the two groups, this could theoretically influence the outcome of the study.

Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. Plast Reconstr Surg. Jun 2006;117(7 Suppl):143S-149S.

In this study, Steed combined data from four previous RCT studies and found that both rhPDGF-BB30µg/g and rhPDGF-BB100µg/g, were more effective in healing wounds compared with placebo gel or good ulcer care alone. Concerns of this study include:

- No information was provided on recurrence of wounds in both the treated and the control group
- No information was provided on inclusion/exclusion criteria of the four RCTs.
- One of the studies included was a phase II trial
- Study did not mention if preparation and application of rhPDGF was the same across all studies.
- No attempt was made to determine quality of studies to see if data could be combined
- No mention of how confounders were handled
- No mention if mitogenic assay was performed to test the potency of the platelet product

Steed DL, Goslen JB, Holloway GA, Malone JM, Bunt TJ, Webster MW. Randomized prospective double-blind trial in healing chronic diabetic foot ulcers. Diabetes Care. 1992;15(11):1598-1604.

The authors concluded that PRP significantly accelerated wound closure in diabetic leg ulcers when administered as part of a comprehensive program for the healing of chronic ulcers. But as noted by other authors, this study has a number of concerns including:

- Age, initial wound area, and wound duration are potential confounders
- PRP treatment could not be considered an isolation in the treatment of chronic wounds a multi-professional treatment program for patients was included in all studies analyzed.

Weed B, Davis MDP, Felty CL, Liedl DA, et al. Autologous platelet lysate product versus placebo in patients with chronic leg ulcerations: a pilot study using a randomized, double-blind, placebo-controlled trial. Wounds. 2004;16(9):1-14.

Though the results of this study revealed that topical autologous platelets had no significant effect on the healing of chronic wounds, there were some areas of concern:

- The study was terminated prematurely due to difficulty in enrolling participants
- The preparation of the platelet product in this study was different from the preparation in other studies
- No mitogenic assay was performed to test the potency of the platelet product. The negative findings in this study could theoretically be due to either the low level of growth factor in the lysate of the lack of sufficient lysate activity.

After reviewing the results on these nine RCTs, some studies showed that PRP increased complete wound healing rates (Knighton et al. 1990; Steed et al.1992; Holloway et al. 1993; Driver et al. 2006; Saad Setta et al. 2011; Steed 2006) while other RCTs studies revealed that PRP did not increase healing rate in the treatment of chronic wounds (Krupski et al. 1991; Stacey et al. 2000; Weed et al. 2004).

Variation among the RCTs

When looking at RCTs, there were a number of variations noted among these studies, which makes it difficult to generalize their findings to our patient population. The following parameters were reviewed.

Duration of wound

All studies except one (Driver et al. 2006) required patients to have a wound for a minimum of eight weeks in order to participate in the study (Driver required a minimum of four weeks). To be consistent, all studies should have the same operational definition when defining wound duration in order to participate in the study.

Preparations

Of the nine RCTs reviewed, two studies evaluated the use of homologous PRP (Steed et al. 1992; Holloway et al. 1993) while the other studies evaluated the use of autologous PRP. CMS believes that it is important to include reviews of articles using homologous PRP preparations because one of the meta-analysis used in this assessment included a study in which the intervention group received homologous PRP (Villela et al. 2010). In this study, the homologous preparation of PRP was found to be more effective in healing diabetic foot ulcers than the comparator group (Holloway et al. 1993). There were no head-to-head comparisons between homologous and autologous preparations, and studies that did use the homologous preparations did not have any complications due to the pooling of serum needed to make this type of preparation.

Also studies documented different amounts of venous blood used to make the PRP preparation. One study required as little as 10cc of venous blood (Saad Setta 2011) while other studies required as much as 240cc of venous blood (Weed et al. 2004). Variance in the amount of venous blood used to make PRP could result in differences in concentrations which could ultimately affect results. And as noted before, some studies performed an analysis to make sure that the collected specimen had an adequate amount of mitogenic activity (Steed et al. 1992; Stacey et al. 2000; Krupski et al. 1991, Knighton et al. 1990), while other studies made no mention of confirming mitogenic activities (Saad Setta et al. 2011; Driver et al. 2006; Holloway et al. 1993; Weed et al. 2004; Steed 2006). The lack of samples containing an adequate amount of mitogenic activity could account for the failure of PRP preparations and the failure of wound closure.

Application

The application of PRP varied between studies. In some studies, PRP and placebo were applied as often as every 12 hours (Krupski et al. 1991; Steed et al. 1992; Weed et al. 2004; Knighton et al. 1990), once a day (Holloway et al. 1993; Steed 2006) or twice weekly (Stacey 2000; Saad Setta et al. 2011; Driver et al. 2006). Also in studies that used a platelet gel preparation, there were different ways of applying it. Man et al. (2001) used a dual syringe method; one syringe to deliver PRP gel and the other syringe to deliver bovine thrombin and calcium chloride. Driver et al. poured platelet gel directly into the wound and then covered it with a dressing. Different schedules of PRP application could make comparisons between studies difficult.

Comparators

There were a myriad of comparators used in the different studies. In the control group, some studies used physiologic (normal/buffered) saline solution (Krupski et al. 1991; Steed et al. 1992; Holloway et al. 1993; Stacey et al. 2000); and some studies used a saline gel dressing (Driver 2006) or a placebo gel (Steed 2006). Also some comparator groups received platelet buffered solution (Knighton et al. 1990), while others received platelet poor-plasma (PPP) (Saad Setta et al. 2011) or PPP plus collagen (Weed et al. 2004). It is difficult to determine if PRP therapy improved wound healing if different comparators are used.

Type of Wound

A number of RCTs addressed patients with only neurotrophic diabetic ulcers (Steed et al. 1992; Holloway et al. 1993; Driver et al. 2006; Saad Setta et al. 2011; Steed 2006), and one study addressed patients with only venous ulcers (Stacey et al. 2000). But in the remaining studies, patients in both the experimental and control group suffered with diabetes, peripheral vascular disease, and venous stasis (Knighton et al. 1990; Krupski et al. 1991; Weed et al. 2004). If there was a disproportionate small amount of one type of wound compared to other types of wounds in the studies that evaluated multiple wounds of different etiologies, stratification of the wound by type should have been performed. If stratification by wound type did not occur, it might lead to a wrong conclusion. Also few studies addressed the use of PRP in patients with pressure ulcers.

In summary, when looking at all of these RCTs collectively, there is little standardization in the parameters being studied. In addition to variation in study design and components, little information was provided on recurrence of ulcers after wound healing, return to previous function, resumption of normal activities as well as improved quality of life.

Other Prospective Studies

This open-label prospective study evaluated the use of PRP in patients with recalcitrant wounds. But issues concerning this study include:

- No use of randomization and control group,
- Open-label study, prone to bias

McAleer JP, Kaplan E, Persich GJ. Efficacy of Autologous Platelet-derived Growth Factors in Chronic Lower Extremity Wounds. J Am Podiatr Med Assoc. Nov-Dec 2006;96(6):482-8.

This prospective cohort study evaluated the efficacy of concentrated autologous PDGF s in chronic lower-extremity wounds. Areas of concern include:

- Lack of randomization and controls

O'Connell SM, Impeduglia T, Hessler K, Wang XJ, Carroll RJ, Dardik H. Autologous platelet-rich fibrin matrix as cell therapy in the healing of chronic wounds. Wound Rep Reg. Nov-Dec 2008;16(6):749-56.

This prospective pilot trial demonstrated that patients with venous as well as non-venous wounds healed with the use of autologous platelet-rich fibrin matrix as cell therapy. But concerns include:

- Small scale pilot study
- No randomization or controls

- The use of fibrin matrix could result in a higher concentration of growth factor when used as a delivery system. According to some authors, the concentration of growth factor could be three times or more higher in the fibrin matrix group than that found in PRP (Yazawa et al. 2003). Due to the high concentration of growth factors, results may not be comparable to non-fibrin PRP products.

In summary, the biggest flaws of this group of studies are the lack of randomizations and controls, as well as small sample size. And like systematic reviews/meta-analysis, little information was provided on recurrence of ulcer after wound healing, return to previous function, resumption of normal activities as well as improved quality of life.

Retrospective Studies

Glover JL, Weingarter MS, Buchbinder DS, Poucher RL, Deitrick GA, Fylling CP. A 4-year outcome-based retrospective study of wound healing and limb salvage in patients with chronic wounds. Adv Wound Care. Jan-Feb 1997;10(1):33-8.

This retrospective study revealed that comprehensive wound care in combination with platelet releasate had higher healing rates and lower amputation rates compared a comprehensive wound care alone.

- Due to the potential for selection bias and inability to control confounders, in general, retrospective studies have lesser evidentiary value
- The authors acknowledged that this population-based study contained uncontrolled variables including the use and choice of antibiotics along with method of administration, duration of therapy, choice of wound dressing, number of attempts to improve arterial blood flow and variations in debridement

Keyser JE. Diabetic wound healing and limb salvage in an outpatient wound care program. South Med J. Mar 1993;86(3):311-7.

This retrospective study showed that diabetic patients who participated in a comprehensive program including a topical growth factor solution of PDWHF had a higher healing rate and were less likely to have amputations compared to diabetic patients who participated in a comprehensive group alone. Concerns of this study include:

- Due to the potential for selection bias and inability to control confounders, in general, retrospective studies have lesser evidentiary value
- Short duration of study
- This study included an aggressive patient education component as well as a strong orthotic component, something that might not be realistic in the current treatment environment

Margolis DJ, Bartus C, Hoffstad O, Malay S, Berlin JA. Effectiveness of recombinant human platelet-derived growth factor for the treatment of diabetic neuropathic foot ulcers. Wound Rep Reg. 2005; 13:531-536.

Using propensity scores as a measure, this retrospective cohort study was able to show that diabetic patients with neuropathic foot ulcers using rhPDGF had a higher healing rate as well as lower amputation rate compared to diabetic patients with neuropathic foot ulcers that did not receive rhPDGF. But like other retrospective studies using propensity scores as a measure, there are a number of potential limitations in the study:

- Due to the potential for selection bias and inability to control confounders, in general, retrospective studies have lesser evidentiary value.
- Propensity score techniques control only for the known covariates that are included in the propensity model. If we exclude covariates that have a substantial effect on the propensity of a subject to receive rhPDGF, then it is possible that within each quintile all known and unknown confounders (e.g., glycemic control, compliance with treatment, etc.) are improperly balanced.
- The degree of group overlap must be substantial, and there is no documentation of how this was achieved.

Margolis DJ, Kantor J, Santanna J, Strom BL, Berlin J. Effectiveness of platelet releasate for the treatment of diabetic neuropathic foot ulcers. Diabetes Care. 2001; 24(3):483-488

In this study the authors concluded that through the use of propensity scores, they were able to demonstrate that PRP was more effective than standard therapy in the treatment of diabetic neuropathic foot ulcers. But there are a number of issues noted in this research:

- Due to the potential for selection bias and inability to control confounders, in general, retrospective studies have lesser evidentiary value.
- There are several limitations on the use to propensity scores. First, propensity score techniques control only the known covariates included in the propensity score model. So it is possible that if a covariate that has a substantial effect on the propensity score is missed, then it is possible that the propensity for PRP treatment within each quintile would not be entirely homogeneous.
- Another limitation of this technique is that whereas the propensity to receive treatment is relatively stable within each quintile, it is not perfectly equal throughout the quintile and residual confounding can occur.
- The study should make sure that the degree of group overlap must be substantial. It was never explained how this was measured.
- The initiation of treatment with PRP is a moving target. Only those who started treatment with PRP by week 12 were considered users of PRP. Some patients did receive PRP after week 12, and these patients would have been classified as having received only standard care, thereby creating the potential for selection bias.
- This study also used varying times of commencement of PRP treatment, resulting in some patients not receiving the full 20-week course of PRP.
- Age and gender are potential confounders

Mazzucco L, Medici D, Serra M, Panizza R, et al. The use of autologous platelet gel to treat difficult-to-heal wounds: a pilot study. Transfusion. July 2004;44(7):1013-18.

In this pilot study the authors concluded that patients with chronic non-healing wounds showed substantial improvement in autologous platelet gel compared to patients treated with conventional therapy. Issues in this study include:

- Due to the potential for selection bias and inability to control confounders, in general, retrospective studies have lesser evidentiary value.
- Small number of participants with Stage III and Stage IV lesions
- Sample size and time required to accomplish the study were not determined in advance
- Evaluators were not blinded

Steenvoorde P, van Doorn LP, Naves C, Oskam J. Use of autologous platelet-rich fibrin on hard-to-heal wounds. J Wound Care. Feb 2008; 17(2):60-3.

This study demonstrated that in patients with chronic wounds, the use of autologous platelet-rich fibrin improved healing rates. But there are a number of issues:

- Due to the potential for selection bias and inability to control confounders, in general, retrospective studies have lesser evidentiary value.
- The use of fibrin as a drug delivery system could result in higher concentrations of growth factors in the platelet concentrate, which could affect results.

Summary

In summary, we conclude that PRP for Medicare beneficiaries with chronic non-healing diabetic, venous and/or pressure wounds is not reasonable and necessary under §1862(a)(1)(A). The available evidence does not allow us to conclude that PRP improves health outcomes in Medicare beneficiaries who have chronic wounds as described in our analytic question above. We also emphasize that the very nature of a retrospective study design makes it prone to confounding and bias. Some of these studies used propensity scores as a method to attempt to provide an unbiased estimation of the treatment effect. But as noted above, the use of propensity scores presents its own methodologic issues. And like the systematic reviews/meta-analysis and RCTs and other prospective studies included in this analysis, little information was provided on recurrence of ulcer after wound healing, return to previous function, resumption of normal activities and improved quality of life.

The systematic reviews/meta-analysis had moderate to severe quality limitations. The RCTs had a marked degree of variation between studies, including type of PRP preparation, production of PRP, documentation of mitogenic activity, lack of standardization of PRP concentration, as well as lack of standardization of the application of PRP. There also was variation in the definition of chronic wounds, as well as choice of comparators. The degree of heterogeneity among the studies questions the validity of the findings, especially those of the systematic reviews and the meta-analyses since they combine multiple RCTs. Findings in other prospective studies were limited due to the lack of randomization and controls. Retrospective studies suffered from selection bias and confounding. The use of propensity scores could potentially negate the findings. Lacci et al. reviewed the literature on PRP treatment of chronic wounds and found that few studies that evaluated the use of PRP on chronic wounds were performed with scientific rigor, although the safety of PRP appears to be validated (Lacci, Dardik 2010).

When looking at the literature, most of the studies did not address recurrence of wounds. And though improved quality of life as well as ability to return to previous function and resumption of normal activity were often mentioned in the medical literature as an objective that can be achieved by treating chronic wounds, the evidence does not confirm this. One study does discuss improved quality of life as an outcome of PRP therapy (Mazzucco et al. 2004). In this study the authors allude to this by mentioning that "almost all patients treated with platelet gel reported significant pain relief, thus bettering their quality of life." However, no measurement tools were used to assess quality of life, nor was there any attempt to include these parameters in the design of the studies. Other RCTs as well as studies with other designs have made similar statements, but have not provided any evidence that successful treatment of chronic wounds results in improved quality of life, return to previous function or resumption of normal activities (Saad Setta et al. 2011, Villela et al. 2010, Trowbridge et al. 2005). A study performed by Spyridakis et al. did show that patients with pilonidal sinus disease who undergo open excision (resulting in an acute wound) and secondary closure using PRP do have a higher quality of life as well as resumption of normal activities. But this NCD concerns PRP treatment of chronic wounds not acute wounds. Also in reference to acute wounds, the charge of this NCD was the evaluation of chronic wounds, so a surveillance of studies on acute wounds was not performed, though a number of studies seemed to indicate that PRP has a positive impact on acute wounds. So, this poses a question of whether this therapy may also be beneficial in chronic wounds.

As mentioned earlier in the analysis section of this NCD, a number of researchers have equated wound size reduction and wound healing trajectory as indirect efficacy measures. A review of the number of studies which looked at these measures failed to show any association with clinically significant health outcomes. CMS is interested in demonstrating that reduction in wound size or healing trajectory does result in some type of patient centered clinically significant health outcomes such as the patient's ability to return to previous function or resumption of normal activity.

Generally, the FDA clears many wound care products, specifically wound dressing devices, under the 510k clearance pathway. As mentioned earlier in this NCD under the FDA Status section, the AutoloGel™ System has the FDA's 510k clearance as a wound dressing device that is intended for the safe and rapid preparation of PRP gel. While the FDA has stated the PRP gel produced from the AutoloGel™ System is suitable for the management of exuding wounds, the FDA has only reviewed the equipment that prepares the PRP gel, and not the clinical safety or effectiveness of the actual gel in regards to the promotion of wound healing. CMS is aware that various stakeholders claim certain benefits related to their product, however the clinical claims of wound healing were not reviewed by the FDA as a condition of clearance or approval, thus were not found to be credible. The FDA's clearance for wound care products actually has a narrow indication as part of wound management. Thus the broader claims of wound healing and other clinical utility measures are not supported by the FDA labeling, and in fact represents gaps in the current evidence. The current FDA cleared label for AutoloGel™ did not answer the relevant question as to if this wound care product does indeed help in the promotion of healing. Understanding that it is nearly impossible to generalize clinical trial data for one type of wound to other types of wounds, the FDA has issued guidance to the general wound-care industry noting that that separate safety and efficacy data should be submitted for each wound type for which a product's indication is sought (FDA 2000).

2. Health Disparities

A review of articles discussed above in this decision memorandum reveals no analysis of PRP clinical outcome by racial or ethnic categories. Any inference about relative benefits of PRP for management of chronic wounds in patients with diabetic, venous or pressure ulcers in specific racial or ethnic groups would be, at best, speculative. CMS also notes the absence of evidence about benefits or harms related to other population classifiers that have been associated historically with healthcare access or outcome disparities, such as gender, sexual orientation, religion, and age, and encourages additional studies in which such associations might be studied.

This lack of evidence about racial and ethnic factors and the response to PRP treatment represents in our view an evidence gap which we encourage trial designers to consider when proposing clinical trial designs for PRP under this NCD. While recognizing that this consideration may complicate the design of appropriate clinical studies, we will nevertheless prefer clinical study proposals in which data on racial and ethnic factors are specifically collected and analyzed.

B. §1862(a)(1)(E) Analysis

When looking at the different types of studies reviewed in this analysis, there are issues that must be addressed. CMS recognizes that the absence of conclusive evidence of benefit does not equate to conclusive evidence of no benefit. CMS also appreciates the significant burden of chronic non-healing wounds on the beneficiary population, which may lead to frustration on the part of patients, their treating practitioners and their caregivers.

Therefore, we believe that it is appropriate to use CED to support the generation of more informative evidence. As explained in the 2006 CED guidance document, cited above, CED facilitates development of additional evidence from approved clinical studies in order to clarify the impact of an item or service on the health outcomes of Medicare beneficiaries. CED enables this additional development of evidence within a research setting where there are added safety, patient protections, monitoring and clinical expertise.

As a foundation for CED, CMS has emphasized three factors relevant to the appropriateness of a CED coverage determination. The first is that the basic safety of the proposed item or service must be assured. In the case of PRP for the treatment of chronic non-healing diabetic, venous and/or pressure wounds, the medical literature has failed to show that adverse event rates are higher or more severe in the PRP treated group compared to the control group.

Second, CMS believes that PRP may have the potential to benefit Medicare beneficiaries. As noted above, PRP has been used in attempts to treat chronic non-healing diabetic, venous and/or pressure wounds. If PRP can be shown that it provides a meaningful clinical benefit for the treatment of chronic wounds, it could potentially lead to improved patient function, and decreased patient dependence on other aspects of the health care system. While we have stated that the evidence as yet is insufficient to support these outcomes, we agree with the importance of investigating these goals and want to encourage future research on these topics through the use of CED.

The third is the difficulty of conducting adequate trials. CMS acknowledges the difficulties that have plagued the development of an informative PRP evidence base and believes that an opportunity should be afforded to address the limitations of previous studies. As noted before a number of RCTs, prospective cohort studies as well as retrospective reviews have been performed. Each of these has a number of flaws that would question the validity of their findings. Also, a number of systematic reviews/meta-analyses have been performed. But since these studies were based on the same RCTs, they would also be subject to the same criticism as RCTs. By identifying issues and concerns of the studies, CMS will assure that appropriate measures are put in place to address these shortcomings.

CMS proposes coverage for PRP for this indication only when PRP is provided under a clinical research study that meets the requirements specified below to assess the effect of PRP for the treatment of chronic non-healing diabetic, venous and/or pressure wounds. The clinical study must address the following questions:

Prospectively, do Medicare beneficiaries that have chronic non-healing diabetic, venous and/or pressure wounds who receive well-defined optimal usual care along with PRP therapy experience clinically significant health outcomes compared to patients who receive well-defined optimal usual care as indicated by addressing at least one of the following:

a. Complete wound healing?
b. Ability to return to previous function and resumption of normal activities?
c. Reduction of wound size or healing trajectory which results in the ability to return to previous function and resumption of normal activities?

Duration of CED coverage for PRP

CMS believes that systematic, protocol-driven data are important to increase the likelihood that beneficiaries achieve improved health outcomes. Care provided under these protocols generally involves greater attention to appropriate patient evaluation and selection, as well as the appropriate application of the technology. These additional data may alter the course of patient treatment based on the best available evidence, and may lead a physician to reconsider the use of the item or service or otherwise alter a patient's management plan, potentially improving health outcomes.

Furthermore, CMS considers the results of all CED clinical studies critical in the evolution of medical technology and in the timely evaluation of the benefit of items and services covered under CED.

CMS proposes that any applications for coverage of PRP in CED studies for this indication pursuant to this NCD must be received and approved by [2 YEARS FROM THE FINAL DM DATE], 2014. If there are no approved clinical studies on this date, this NCD will expire and coverage of PRP for chronic non-healing diabetic, venous and/or pressure wounds will revert to the coverage policy in effect prior to the issuance of the final decision memorandum for this NCD.

Disparities

Studies performed in the United States should also provide evidence about benefits or harms related to other population classifiers that have been associated historically with healthcare access or outcome disparities, such as gender, age, sexual orientation and religion, and encourages additional studies in which such associations might be studied. We find it helpful when clinical studies include data on racial and ethnic factors where they are relevant to the conclusions that may be drawn about the impact of the investigational item or service.

IX. Conclusion

The Centers for Medicare & Medicare Services (CMS) believes, based on its review, that the available evidence does not permit us to conclude that use of autologous PRP (PRP) improves beneficiary health outcomes in patients with chronic diabetic ulcers, pressure ulcers and venous ulcers. We therefore propose that PRP used to treat chronic non-healing diabetic, venous and/or pressure wounds be covered under Coverage with Evidence Development (CED) under §1862(a)(1)(E) of the Act

CMS recognizes that chronic non-healing diabetic, venous and/or pressure wounds are an important cause of disability and burden for beneficiaries and society. More rigorous study of PRP therapy may yet produce evidence of improved health benefit for patients with chronic non-healing diabetic, venous and/or pressure wounds.

The patient is enrolled in a randomized clinical trial that addresses the following questions using validated and reliable methods of evaluation. Clinical study applications for coverage pursuant to this NCD must be received by [2 YEARS FROM THE DATE OF FINAL DM ISSUANCE], 2014.

The clinical research study must meet the requirements specified below to assess the effect of PRP for the treatment of chronic non-healing diabetic, venous and/or pressure wounds. The clinical study must address:

Prospectively, do Medicare beneficiaries that have chronic non-healing diabetic, venous and/or pressure wounds who receive well-defined optimal usual care along with PRP therapy, experience clinically significant health outcomes compared to patients who receive well-defined optimal usual care for chronic non-healing diabetic, venous and/or pressure wounds as indicated by addressing at least one of the following:

a. Complete wound healing?
b. Ability to return to previous function and resumption of normal activities?
c. Reduction of wound size or healing trajectory which results in the patient's ability to return to previous function and resumption of normal activities?

The required randomized clinical trial (RCT) of PRP must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the RCT is to test whether PRP improves the participants' health outcomes.
b. The RCT is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The RCT does not unjustifiably duplicate existing studies.
d. The RCT design is appropriate to answer the research question being asked in the study.
e. The RCT is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The RCT is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46.
g. All aspects of the RCT are conducted according to appropriate standards of scientific integrity set by The International Committee of Medical Journal Editors

(http://www.icmje.org).
h. The RCT has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for coverage with evidence development.
i. The RCT is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
j. The RCT is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The RCT study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors

(http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
l. The RCT protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
m. The RCT protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with §1142 of the Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

We are requesting public comments to this proposed decision pursuant to § §1862(l) of the Act. After consideration of the public comments, we will issue a final determination responding to the public comments consistent with §1862(l)(3) of the Act.

APPENDIX A

General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-RTCs and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

APPENDIX B

Tables
(Summaries of Literature Analyses) **Table 1: Excluded Studies**

Study*	Reason for exclusion**
Akingboye 2010	Review article discusses concepts on the use of PRP in treating chronic ulcers
Almdahl 2011	Discusses PRP in acute wounds
Alsousou 2009	Review article discusses the biology of PRP
Anitua 2004	Review article discusses the biology of PRP
Anitua 2007	Review article discusses the impact of PRP in the medical field
Armstrong 1998	Review article on diabetic ulcers

Study*	Reason for exclusion**
Arora 2009	Review article discusses the biology of PRP
Atri 1990	Homologous platelet factors were used in the study
Babbush 2003	Discusses use of PRP in patients undergoing oral reconstruction
Balbo 2010	Discusses the use of PRP in patients with loss of finger substance
Belli 2005	Discusses PRP in combination with bovine derived HA xenograft
Bernuzzi 2010	Study only looked at percentage of healed wound
Brady 2006	Discusses use of PRP in bariatric surgery
Braund 2007	Review article discusses the biology of PRP
Brown 2006	Discusses use of PRP in rhytidectomy surgery
Buchwald 2008	Discusses PRP in acute wounds
Camargo 2005	Discusses use of PRP in combination with bovine porous bone mineral (BPBM)
Carreon 2005	Discussed the use of PRP in patients undergoing lumbar fusion surgery
Castro 2004	Discussed the use of PRP in patients undergoing lumbar fusion surgery

Study*	Reason for exclusion**
Cervelli 2010	Discusses PRP and hyaluronic acid
Cervelli 2010	Discusses PRP, stem cells, adipose tissue and Hyaluronic acid
Cervelli 2011	Describes use of stromal vascular fraction, grafting with PRP
Christgau 2006	Discusses use of PRP in patients with intra-body defects
Cooper 1994	Review article discusses the biology of PRP
Crovetti 2004	Study only looked at reduction in wound size
de Leon 2011	Study only looked at percentage of healed wound
Della Valle 2003	Discusses use of PRP in patients undergoing oral surgery
Dougherty 2008	Cost-effectiveness model using PRP
Englert 2008	Discusses PRP in acute wounds
Everts 2006	Discusses use of PRP in patient undergoing total knee arthroplasty
Everts 2006	Review article discusses the biology of PRP
Fanning 2007	Discusses PRP in acute wounds

Study*	Reason for exclusion**
Ficarelli 2008	Case review discussing the use of PRP in patient with chronic venous leg ulcer
Franchini 2005	Discusses use of PRP in patients undergoing bone reconstructive surgery
Frechette 2009	Review article discusses the biology of PRP
Frykberg 2010	Discussed wound volume reduction not wound healing
Gardner 2006	Discusses use of PRP in patient undergoing total knee arthroplasty
Gottrup 2010	Discussed recommendation of outcomes for clinical wound collection
Grant 2005	Discusses use of PRP in patients with diabetic neuropathic fractures
Green 1998	Discusses PRP in acute wounds
Griffin 2004	Discusses use of PRP for treatment of gingival recession
Gurvich 2008	Discusses use of Negative Pressure Wound Therapy in conjunction with PRP
Hanna 2004	Discusses use of PRP in combination with xenograft
Huang 2005	Discusses use of PRP in patients undergoing dental procedure
Jenis 2006	Discussed the use of PRP in patients undergoing lumbar fusion surgery

Study*	Reason for exclusion**
Kassolis 2005	Discusses use of PRP in patients undergoing subantral sinus augmentation
Kitoh 2004	Discusses use of PRP in combination with mast stem cells
Klayman 2006	Discusses combined use of PRP and vacuum assisted closure procedures
Klayman 2006	Discusses use of Negative Pressure Wound Therapy in conjunction with PRP
Lacci 2010	Review article discusses concepts on the use of PRP in treating chronic ulcers
Langer 2009	Systematic review of economic evaluations of PRP products in patients with chronic wounds
Maiorana 2003	Discusses use of PRP in combination with an organic bovine mineral xenograft
Marx 2004	Discusses use of PRP in dental procedures
McAleer 2006	Review article on the use of PRP
Mendez 2006	Discusses use of PRP in patients undergoing alveoloplasty
Okuda 2005	Discusses use of PRP for dental procedure
Ouyang 2006	Discusses use of PRP during dental procedure
Peitramaggiori 2006	Review article discusses the biology of PRP

Study*	Reason for exclusion**
Philippart 2005	Discusses use of PRP in combination with an organic bovine mineral xenograft
Pomerantz 2005	Discusses use of PRP for endoscopic sinus surgery
Raghoebar 2005	Discusses use of PRP in patients undergoing sinus surgery
Roukis 2006	Review of the medical literature on different PRP products
Rozman 2007	Review article discusses the biology of PRP
Sammartino 2005	Discusses use of PRP in patients undergoing surgery for periodontal defect
Scevola 2010	Discussed wound volume reduction not wound healing
Schade 2008	Discusses the use of PRP along with split-thickness grafts
Sell 2011	This case report study looked only at percentage of healed wound, not complete healing, and no correlation to return to function or resumption of normal activity
Senet 2003	Study involved the use of frozen autologous platelet solution (FAP)
Senet 2004	Letter to editor
Simon 2004	Discusses use of PRP for osseous regeneration
Smith 2009	Review article discusses the biology of PRP

Study*	Reason for exclusion**
Soomekh 2011	Review article on the use of PRP
Stammers 2009	Review article on the medical uses of PRP
Steigmann 2005	Discusses use of PRP in patients undergoing sinus lift procedure
Trowbridge 2005	Discusses use of PRP in patients undergoing CABG
van der Hagen 2009	Retrospective study on use of PRP in patients with anal fistulas
Vick 2006	Discusses use of PRP in blepharoplasty procedures
Whitlow 2008	Discusses barriers to use of PRP
Whitman 1997	Discusses use of PRP for dental procedure
Yol 2008	Discussed the use of PRP in colonic anastomosis

**This is a partial list of studies.*
***Multiple reasons for exclusion may exist, but only one is listed.*

Table 2: Randomized Clinical Trials

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
1. Driver, Hanft, Fylling, Beriou 2006.		PRP gel was used in the intervention group, while the control group used saline gel dressings		Using an Intent to Treat Analysis (ITT) of the 72 participants, 13 of 40 patients (32.5%) in the PRP gel and nine of 32 patients	

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
A Prospective, Randomized, Controlled Trial of Autologous Platelet-rich Plasma Gel for the Treatment of Diabetic Foot Ulcers.	Prospective, randomized, controlled, double-blinded, multicenter trial/Outcomes included measures of safety as well as incidence of complete healing and healing rate adjusted for wound size, as well as incidence of wound recidivism among healed ulcers during a 3-month follow-up period. Evaluation was biweekly for 12 weeks or until healing occurred. Patient had to have wound for at least four weeks to be included in the study.		Eligibility criteria included persons with type I or type II diabetes. Between the ages of 18 and 95 with an ulcer of at least 4-weeks' duration. N = 72 patients that met the inclusion criteria, 40 in the intervention group and 32 in the control group. Mean age in intervention group-56.4, mean age in control group 57.5 (P = NS). % of males intervention/control group 80%/81.4 respectively (P = NS).	(28.1%) in the control group had completely healed wounds after 12 weeks (P = 0.79). Because the authors felt that the ITT analysis results did not reflect previous clinical outcomes, an independent audit was performed. This resulted in the elimination of 32 participants due to protocol violations and failure to complete treatment. The final analysis was based on 19 patients in intervention group and 21 patients in control group. Based on this new analysis, 13 of 19 (68.4%) patients in PRP gel and nine out of 21 (42.9%) patients in the control group healed (P = 0.125). After adjusting for wound size, more patients in the PRP group had complete healing (81.3%) compared to patients in the control group (42.1%) s, respectively (P = 0.036.	The authors concluded that PRP gel is safe for use in the treatment of non-healing diabetic foot ulcers. They also note that in the most common size of diabetic foot ulcers (≤7.0 cm2 in area and ≤2.0 cm3 in volume); PRP gel-treated wounds are also significantly more likely to heal than control gel treated wounds. Treating wounds with PRP or saline gel resulted in healing in approximately six weeks, but in the most common wound sizes, almost twice as many PRP treated wounds healed in that timeframe.
2. Holloway, Steed, DeMarco, Masumoto, et al. 1993. A randomized, controlled, multicenter, dose response trial of activated platelet supernatant, topical CT-102in chronic non-healing, diabetic wounds.		Participants were randomized to either the control group (normal saline) or to the PDWHF group (Platelet-derived Wound Healing Formulary, Homologous Group).	N = 70; They were randomized to either placebo group or to one of three dilution groups-0.01, 0.1, or 0.033. Baseline characteristics failed to show any differences between the three dilutions and placebo group when comparing patient age, sex distribution, wound grade or severity score. Average age varied between 59 and 62 between the four groups.	Wound healing was higher in all groups of PDWHF dilution compared to control group. 29% had complete healing in the control group, while in the PDWHF group, healing occurred in 80%, 62%, and 52% in the 0.01, 0.033 and 0.1 dilution groups respectively (P = 0.02). No statistical difference was noted among the drug solutions. The median time for complete healing in the PDWHF group was 140 days, but the median time for complete healing in the control group could not be determined since less than half of the patients in this group healed.	The use of PDWHF was more effective than placebo in healing wounds

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
	Randomized, prospective, double-blind, placebo-controlled, multi-center, dose response trial. Primary outcome was healed ulcers defined as 100% epithelialized. Functional assessment tool that looked at degree of epithelialization, drainage, and need for dressing change, ranging from Level 1 < 100% epithelialization with drainage/and the need to change dressing, to Level 4 = 100% epithelialization no drainage/no need to change dressing. Patient had to have wound for at least eight weeks to be included in the study.				
3. Knighton, Ciresi, Fiegl, Schumerth, Butler, Cerra 1990. Stimulation of repair in chronic, non-healing cutaneous ulcers using platelet-derived wound healing formula.		PDWHF was use in the treatment group, while control group received platelet-buffered solution. After eight weeks, those in the control group received the PDWHF.	N = 32; 16 patients were randomized to each group. Average age in intervention group was 64; average age in control group was 62.	After eight weeks, 17 out of 21 wounds (81%) of patients in treatment group achieved epithelialization compared to two of 13 (15%) in the control group ($P < 0.0001$). After crossover to treatment with PDWHF, all the patients in the control group had epithelialization in an average of 7.1 weeks	Results of study demonstrate that a significant increase in the rate of epithelialization in wounds treated with PDWHF.

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
	Randomized Prospective, Double-blind Placebo controlled crossover study. After eight weeks, patient in control group would be placed in treatment group. Endpoint was epithelialization of the wound. Total Wound Severity Scores (TWSS) was used to classify severity of wound based on clinical, anatomic, and measured wound and patient variables. Patient had to have wound for at least eight weeks to be included in the study.				
4. Krupski, Reilly, Perez, Moss, Crombleholme, Rapp 1991. A prospective randomized trial of autologous platelet-derived wound healing factors for treatment of chronic non-healing wounds: A preliminary report.	Randomized, prospective double-blind, placebo-controlled study. Outcome of interest was wounds healed-wounds were considered healed when they were completely covered with new epithelium by visual inspection. To be eligible for study, Patient had to have wound for at least eight weeks to be included in the study.	Patients were randomized to either control group (placebo) which received physiologic saline or to the autologous PDWHF group. All patients received standard surgical and supportive care.	N = 18 (all males); eight in control group with nine wounds, and 10 in the PDWHF group with 17 wounds. Ages ranged from 57 to 75 (mean, 66.4 +/- 4.9 years). On average wounds were present for 5.5 months +/- 4.3 months. 75% of patients had DM, 72% had occlusive PVD, and 28% had venous disease. Demographics and laboratory values were equivalent between both groups.	Average duration of therapy was 10.1 +/- 2.7 weeks (median 12, mode 12); three of nine (33%) in the control group had complete healing, while four of 17 (24%) in the PDWHF had complete healing. No significant difference was observed in comparing either wounds healed or patients healed.	The author concluded that autologous PDWHF failed to provide additional benefit over traditional therapy for healing chronic non-healing cutaneous wounds

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
5. Saad Setta, Elshahat, Elsherbiny, Massoud, Safe 2011. Platelet-rich plasma versus platelet-poor plasma in the management of chronic diabetic foot ulcers: a comparative study.	RTC. Wound healing was the outcome of interest, performed by measuring wound dimensions	PRP gel was used in the intervention group, while platelet-poor plasma was used in the control group.	Eligibility criteria included persons with type I or type II diabetes. Between the ages of 40 and 60 with an ulcer of at least 12 weeks' duration. N = 24 patients that met the inclusion criteria, 12 in the intervention group and 12 in the control group.	Mean healing time in the PRP group was 11.5 weeks, while healing time in the platelet-poor plasma group was 17 weeks (P < 0.005).	Healing in the PRP group was significantly faster than in the platelet-poor plasma group
6. Stacey, Mata, Trengove, Mather 2000. Randomized double -blind placebo controlled trial of topical autologous platelet lysate in venous ulcer healing.	Randomized, prospective, double-blind, placebo controlled study. Outcome of interest was healing based on photographs, planimetry, and tracings	Intervention group received a preparation of autologous platelet lysate. Control group received a buffered solution. Both groups received solutions twice per week for up to nine months in combination with standard compression bandages.	N = 86; 42 patients in the intervention group and 44 patients in the control group. The two groups were equivalent in age and sex distribution. Average duration of ulcer in both groups was 12 weeks. Average age 70 for placebo group and 72 for intervention group.	34 of 44 subjects (77%) in the placebo group had complete healing, while 33 of 42 subjects (79%) in the intervention group had complete healing. There was no difference between the two groups. The use of topical platelet lysate had no significant influence on venous ulcer healing	Platelet lysate as used in the study had no influence on the healing of chronic venous ulcers.
7. Steed. 2006. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers.	Randomized prospective blinded clinical trials	rhPDGF-BB30µg/g and rhPDGF-BB100µg/g, was compared with placebo gel or good ulcer care.	N = 922 type I or type II diabetic patients, ranging in age from 23 to 93 years, median age 59. Of the 922 patients treated, 874 (95%) had baseline ulcer areas that were less than or equal to 10 cm2		The authors concluded that PDGF once daily was effective in healing chronic diabetic neuropathic ulcers when used in conjunction with good would care

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
				The incidence of complete healing in the first study in all patients treated with rhPDGF-BB30µg/g was 48% compared to 25% for those treated with placebo gel; the incidence of complete healing in the second study in all patients treated with rhPDGF-BB100µg/g was 50% compared to 36% for those treated with rhPDGF-BB30µg/g, and those receiving placebo gel. Results of treatment with rhPDGF-BB100µg/g gel were statistically significantly different from placebo gel results (P = 0.01). In the third study which was designed to compare placebo gel to good wound care alone, the overall incidence of complete healing in all patients was 44% for patients receiving rhPDGF-BB100µg/g, compared with 36% for those receiving placebo gel and 22% for those receiving good ulcer care alone. In the fourth study, the incidence of complete ulcer healing in the rhPDGF-BB100µg/g was 36% and that for the good ulcer care group alone was 32%.	
8. Steed, Goslen, Holloway, Malone, Bunt, Webster 1992. Randomized prospective double-blind trial in healing chronic diabetic foot ulcers.		Participants were randomized to either the control group (normal saline) or to the PDWHF group (Platelet-derived Wound Healing Formulary, Homologous Group).		In the control group only one of six ulcers healed by week 20, but in the PDWHF group five of seven ulcers healed within 15 weeks.	The authors concluded that patients with diabetic neurotrophic ulcers treated with PDWHF have a better clinical response than diabetic patients with neurotrophic ulcers treated with placebo.

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
	Randomized, prospective double-blind trial. Primary outcome was healed ulcers defined as 100% epithelialized. Functional assessment tool which at degree of epithelialization, drainage, and need for dressing change, ranging from Level 1 < 100% epithelialization with drainage/need to change dressing, to Level 4 100% epithelialization no drainage/no need to change dressing. Patient had to have wound for at least eight weeks to be included in the study.		N = 13 (9 males, four females), seven in PDWHF group ranging in age from 39-75 (mean age of 59), and six in the control group ranging in age from 41-74 (mean age of 54). All participants were diabetic with neurotrophic ulcers on lower extremities that had not healed after eight weeks of standard treatment. Baseline characteristics were the same between both groups except treatment group had DM longer than control group (26 versus 10 years)		
9. Weed, Davis, Felty, Liedl, et al. 2004. Autologous platelet lysate product versus placebo in patients with chronic leg ulceration: A pilot study using a randomized, double-blind, placebo-controlled trial.	Single-centered, prospective, randomized, double-blind, placebo-controlled trial. Outcome of interest was complete healing (100% epithelialization of the entire target ulcer) as assessed by clinical exam and photography.	Autologous platelet lysate factors added to collagen (treatment group) was compared to platelet poor plasma plus collagen (control group). After 12 weeks, there was a washout period of two weeks. Patients whose ulcers had not healed were then assigned to receive whichever treatment they had not received in the previous 12 weeks.	N = 26; Treatment group n = 15, control group n = 11. Patients in the study included those with non-healing ulcers of the lower extremity for more than eight weeks. Baseline characteristics fail to reveal any differences between both groups. Average in intervention group was 68; average age in placebo group was 58.		Wound healing rate was not significantly different between the treatment and the placebo group.

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
				During the first 12 weeks, in the treatment group nine of 15 (60%) patients healed, while four of 11 (36%) in the control group healed. There was not a statistically significant difference between the proportion healed in these two groups at 12 weeks (P = 0.68). After a two-week washout period, in the treatment group two (29%) patients healed, while two (33%) in the control group healed. There was not a statistically significant difference between the proportion healed in these two groups at the end of the second 12 week period (P = 0.99). Throughout the study, 11 patients (42%) healed with platelet lysate, six (23%) healed with placebo treatment, and nine (35%) failed to heal. In the analysis using both time periods, there was not a statistical difference between treatment groups in the proportion healed (P = 0.31).	

Table 3: Other Prospective Studies

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
1. Gurgen, 2008.	Open label prospective study. The primary endpoint was time to healing, and the secondary endpoint was reduction in ulcer size if wounds had not healed.	PRP	Population of 13 patients with 14 recalcitrant leg and foot ulcers; three females and 10 males with an	On day seven after treatment, ulcer size had reduced by an average of 31.4% (range 2.1%-77.7%) in 11 of 14 wounds. After 28 days, one wound had healed completely. Of the	The use of PRP can be an option when treating recalcitrant wounds of differing aetiologies

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
Treatment of Chronic Wounds with Autologous Platelet-rich Plasma.			average age of 52.1 years (range 35-76). The largest groups of wound diagnoses were venous leg ulcers (n = 6) and diabetic foot ulcers (n = 3). The average duration of the ulcers was 6.8 years (range 2 months-21 years) of various aetiologies	remaining ulcers, 12 had decreased in size to an average of 55.2% (range 6.2%-80%) of their original size. All of those were clinically assessed as improved. Seven (50%) of the ulcers healed within an average of 153 days.	
2. McAleer, Kaplan, Persich, 2006. Efficacy of Autologous Platelet-derived Growth Factors in Chronic Lower Extremity Wounds.	Prospective study with no randomization or control group/Wound closure with complete epithelialization, and percent of wound closure	PDGF and fibrin, along with non-adhering pressure dressing	Population included 24 patients with 33 chronic wounds (mean age 61.9). 13 females and 11 males; three patients had venous ulcers, two patients had decubitus ulcers, five had arterial insufficiency, eight patients had ulcers due to diabetes, and six had diabetes with neuropathic pathology	20 wounds achieved wound closure and epithelialization, three wounds achieved 75% or greater closure, two wounds achieved 50% to 74% closure, and two wounds achieved 25 to 49% closure. five wounds showed no improvement. Mean time to complete closure was 11.15 weeks	PDGF was effective in a variety of diverse patient populations
3. O'Connell, Impeduglia, Hessler, Wang, Carroll, **Dardik 2008.** Autologous platelet-rich fibrin matrix as cell therapy in the	Prospective, pilot trial/The primary endpoints were percent and rate of complete closure. The study duration was 12	Autologous platelet-rich fibrin matrix membrane, along with compression dressing	Study group consisted of 12 patients with 17 venous leg ulcers (VLU) and nine patients with 13 non -venous lower extremity ulcers. Eligible patients had to be between 18 and 85 year of age.	64.7% of treated ulcers (66.7% of patients) closed within 16 weeks and an additional two ulcers reached 75% closure (secondary endpoint). In the non-venous ulcer group 44% of the ulcers treated with autologous platelet-rich fibrin had complete closure (31% of treated ulcers). No ulcers reopened. Mean time to complete closure	The authors concluded that autologous PRFM represents a safe, convenient easy-to-use adjuvant therapy that shows significant potential for closing of chronic leg ulcers

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
healing of chronic lower -extremity ulcers.	weeks with 1-month follow-up. Primary efficacy endpoint was the incidence and time to complete closure in the absence of drainage. Secondary endpoints were the incidence and time of 75% closure. Digital photography and computer planimetry used to determine complete healing.			for venous ulcers was 7.1 weeks (median 6 weeks).	
4. Scevola, Nicoletti, Brenta, Isernia, Maestri, Faga 2010. Allogenic Platelet gel in the Treatment of Pressure Ulcers; A pilot study.	A prospective randomized trial	Allogenic platelet gel compared to best treatment approach	Study group consisted of 13 spinal cord patients with 16 pressure ulcers over a 20 month period.	At time period T5 (10 weeks), 15 out of 16 ulcers demonstrated clinical improvement. At time period T6 (14 weeks), only 11 ulcers remained in the study. No statistical differences in volume reduction.	Allogenic platelet gel can be used as a starter for any halted healing process within the first two weeks of treatment

Table 4: Retrospective Studies

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
1. Margolis, Kantor, Santanna, Strom, Berlin, 2001		Platelet releasate (PR), an autologous product, was used in the study and compared to standard care.	Database maintained by Curative Health Services; In PR group, n = 6253; In non-PR group, n = 20,347; Patients were	Patients treated with PR were more likely to have larger wounds, older	PR was found to be effective in the treatment of diabetic foot ulcers; PR was found to be more likely to be used in more severe wounds and is more effective than standard care in these

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
Effectiveness of Platelet Releasate for the Treatment of Diabetic Neuropathic Foot Ulcers.	Retrospective cohort study, using logistic regression to develop propensity scores to control for treatment selection bias/Outcome of interest (end point) was quintile specific healing rates within 32 weeks of care after the first wound care center visit.		stratified into quintiles based on the distribution of propensity scores.	wounds, and wounds of higher grade. The overall proportion of patients healed by 32 weeks of care showed a downward trend with the increasing group number; that is, those patients most likely to receive PR were least likely to heal independent of treatment effect. Patients treated with PR were more likely to heal than those patients not treated with PR for all five propensity score strata. Further ad hoc analysis showed that the effect of PR was greatest for those patients with larger wounds of higher grade.	severe wounds. The authors also noted that there was significant interaction between the effectiveness of PR and the propensity score quintile, as well as the limitations of using propensity scores.
2. Glover, Weingarten, Buchbinder, Poucher, Deitrick, Fylling 1997. A 4 year outcomes-base retrospective study of wound healing and limb salvage in patients with chronic wounds.	Multi-center, retrospective Trial/Outcome of interest is wound healing, defined as 100% epithelialization with minimal of no drainage, and limb salvage	Patients were placed into two groups: Wound healing with comprehensive wound care alone (CWC), and wound care healing with comprehensive care plus platelet releasate (CWC+PR)	N = 3830; 1019 in the CWC group and 2811 in the CWC+PR group. Average in the CWC group was 64.7 and in the CWC+PR was 64.5 P = 0.71.	Healing rates were higher in the CWC+PR group than in the CWC alone group (P < 0.0001). Also amputation rates were lower in the CWC+PR group compared to the CWC along group (P < 0.00005).	Authors concluded that patients treated with CWC+PR had higher rates of healing wounds, and increased limb salvage for most wounds compared to patients treated with CWC.
3. Keyser. 1993.		Comprehensive program including PDWHF			Diabetic wound patients benefited from treatment with PRP

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
Diabetic wound healing and limb salvage in an outpatient wound care program.	Retrospective study/Outcome of interest is wound healing and limb salvage. Wounds were assessed using the Wound Care Center Grading System, and measurements were standardized. Volume was calculated by multiplying area by depth.		N = 54 diabetic patients with 86 wounds, with an average wound duration of eight months. Average age of participant was 58.8 years,	Healing occurred in 88% in 16 weeks; of the wound recommended for amputation, 93% were able to be salvaged. And though wounds of larger area and volume were of higher grade, the percentage of wounds that healed did not differ from the percentage of less severe wounds that healed.	
4. Margolis, Bartus, Hoffstad, Malay, Berlin 2005. Effectiveness of recombinant human platelet-derived growth factor for the treatment of diabetic neuropathic foot ulcers.	Retrospective cohort study using logistic regression to develop propensity scores that control for selection bias/ Outcomes of interest included quintile specific healing and amputation rate	rhPDGF was used in the intervention group compared to patients who did not receive rhPDGF	N = 24,898, of this number rhPDGF = 2,394, the rest were in the non-rhPDGF group. Patients were stratified into quintile groups based on propensity scores	The percentages and RR of wounds healed by rhPDGF were 35% vs. 26% (RR 1.34), 33% vs. 26 (RR 1.28), 27% vs. 25% (RR 1.1), 37% vs. 26% (RR 1.43), and 33% vs. 26% (RR1.32) from group 1 to group 5. The percentages and RR of amputations by rhPDGF were 1.1% vs. 1.5% (RR 0.71), 5% vs. 4.4 (RR 1.14), 5.7% vs. 7.8% (RR 0.73), 4.5% vs. 9.8% (RR 0.46), and 4.9% vs. 6.4% (RR 0.65) from groups 1 through 5.	The authors concluded that within the limits of the study, rhPDGF was more effective than standard therapy in both helping a wound heal and in preventing amputation.
5. Mazzucco, Medici, Serra, Panizza, Rivara, Orecchia, et al. 2004.	Retrospective study. Patients treated with PLT gel were retrospectively compared with patients having similar lesions but undergoing conventional treatment./Outcomes included healing rate, the length of hospital	PLT gel which was prepared by treating autologous Platelet concentrates with autologous thrombin.		In Group 1, patients treated with PLT gel achieved 100% healing in 3.5 weeks compared to conventional treatment which took 6.0 weeks (P = 0.0002). Difference in median hospital stay was 31.5 days for PLT treated patients, and 52.5 days for control group (P = 0.0001).	The authors concluded that Patients with chronic non-healing wounds showed substantial improvement when treated with PLT gel lesion dressings.

Authors / Title	Study Design / Outcomes	Intervention	Demographics	Results	Conclusions
The use of autologous platelet gel to treat difficult-to-heal wounds: a pilot study.	stay, and/or the time required to bring about adequate tissue regeneration in order to undergo reconstructive plastic surgery		Two groups: Group 1 had 22 patients with dehiscent sternal wounds (10 treated and 12 controls) and Group two had 31 patients with necrotic skin ulcers (17 treated and 14 controls). For sternal wound patients mean age in treatment group was 64, for control 66; for necrotic skin group mean age in treatment group 61, mean age in control group was 63	In Group 2, patients treated with PLT gel had shorter time required to have surgery (median, 15.0 vs. 35.5 wks; P < 0.0001).	
6. Steenvoorde, van Door, Naves, Oskar, 2008. Use of autologous platelet-rich fibrin on hard-to-heal wounds.	Retrospective open label study/Outcomes included wound closure with no recurrence reduction in wound diameter, and occurrence of adverse events.	Platelet-rich fibrin	Population consisted of 12 patients with 13 wounds (four males and eight females,- mean age of 60.5 years (range 38–89). The mean wound duration before treatment was 15.7 months (range 1–48).	8 (62%) of wounds closed and three (23%) of wounds reduced in diameter by up to 66%. Two (15%) of wounds did not reduce in size, although one of these did reduce in depth. The mean treatment period was 4.2 weeks (range one week to three months).	The authors concluded that treatment with platelet-rich fibrin in patients with chronic wounds is feasible

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